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CALCIFICATION AS A DIAGNOSTIC SIGN OF SYPHILITIC AORTITIS

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CALCIFICATION of the aorta, particularly the knob, is commonly seen in roentgen studies of the chest. Little attention is usually paid to this finding other than to note its presence. Calcification of the ascending aorta alone, or with calcification of the knob, was noticed with sufficient regularity in cases of syphilitic aortitis studied roentgenologically at the Los Angeles County General Hospital to stimulate interest in its significance. Of thirty-eight unselected cases of syphilitic aortitis referred for study during a nine-month period, nineteen (50 per cent) showed calcification of the thoracic aorta and fifteen (39.4 per cent) showed calcification of the ascending aorta alone.

In atherosclerosis of the aorta the most advanced lesions are found usually in the abdominal portion. The thoracic aorta is usually less severely affected, but it is frequently more or less markedly involved. Atheromatosis usually begins at the mouths of the intercostal arteries and spreads peripherally. The base of the aorta is often relatively intact except in very severe cases.[1-4]

The significance of atherosclerosis in relation to syphilitic aortitis has not been well appreciated in spite of the fact that as early as 1925 Anitschkow[5] pointed out that syphilitic infection of the aortic wall predisposed to the development of atheromatous lesions in the intima. In the late stages of this process this is often very evident. The intima is very thick and fibrous, with fatty spots in its depth that tend to disintegrate and to become calcified.

Atheromatosis with calcification of the aorta has usually been considered as a coincidental finding. Christian[6] has stated that "calcification and intimal ulceration are infrequent in syphilitic aortitis, but often arteriosclerosis is combined, and in the arteriosclerotic lesions calcification and ulceration are frequent." Boyd[2] was struck by the frequency with which atheromatous lesions are found in the intima and stated that, although syphilis is not a direct cause of atheroma, it may act as a predisposing factor. Bell[3] did not mention the connection between

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arteriosclerosis and syphilitic aortitis other than to state that "when arteriosclerotic changes are also present (atheroma and calcification) the picture becomes complicated and more difficult to recognize." Mallory,[4] on the other hand, in a discussion of a case stated that "the aorta was markedly sclerotic, diffusely dilated, wrinkled, and scarred in spots between the atheromatous plaques. The entire process was most marked in the thoracic portion of the aorta, diminishing as one proceeded toward the abdominal portion, which is characteristic of syphilis and in contrast to ordinary arteriosclerosis." Forbus[7] has pointed out also that the syphilitic process stops quite abruptly at the lower level of the arch, a common and characteristic occurrence.

The characteristic findings in the aorta in syphilis and arteriosclerosis can be illustrated by the two brief case histories which follow.

Fig. 1 is an illustration of the aorta of a 69-year-old patient with a diagnosis of syphilitic aortitis. The aorta shows the typical longitudinal "tree-bark" wrinkling and atheromatosis which involved the ascending aorta and arch and abruptly ended at the junction of the arch and descending aorta. Fig. 2 is a post-mortem x-ray film of this aorta showing the calcification laid down in an interlacing manner which follows the pattern of longitudinal wrinkling. The interlacing network, when caught on end, produces a linear shadow, which explains the linear type of calcification seen in the ascending aorta in ante-mortem x-ray films. Fig. 3 is the ante-mortem roentgenogram of the patient whose aorta is depicted in Figs. 1 and 2.

Fig. 4 is an illustration of the aorta of a 70-year-old patient with typical atherosclerosis of the aorta. The ascending aorta is smooth and free of atheromata. In the arch and descending aorta the atheromatosis is marked. Fig. 5 is the post-mortem film of this aorta showing spotty calcified plaques in the arch with calcification most marked about the orifices of the arteries as they leave the aorta.

With the difference in localization of the atheromatosis in the aorta in arteriosclerosis and syphilis, it was felt that demonstration of calcification in the different portions of the aorta should be of value in the differential diagnosis of these two conditions. Review of the literature and the textbooks of roentgenology has revealed little comment or agreement on this subject. Mallory and Schatzki[4] and Bland and Mallory[8] have stated that calcification is an important clue to the presence of syphilitic aortitis and more indicative of the disease than against it. Sproul[9] mentioned identification of calcification in the aorta and showed a case with marked involvement of the ascending aorta but made no special comment. Schwedel[10] stated that calcification of the aortic arch is due most often to arteriosclerosis, although it is frequently associated with syphilitic aortitis. He felt that calcification may be considered as evidence of past damage but is not of itself diagnostic of syphilitic aortitis, nor of prognostic significance. He also pointed out that calcification of the aorta is absent in the stage of dynamic dilation but is not infrequent when the static stage is reached. Roessler[11] stated that "it may be a difficult matter at necropsy to distinguish between atheroma of the aorta and syphilitic aortitis because syphilitic aortitis is very frequently accompanied by atheromatous changes in the aorta." He

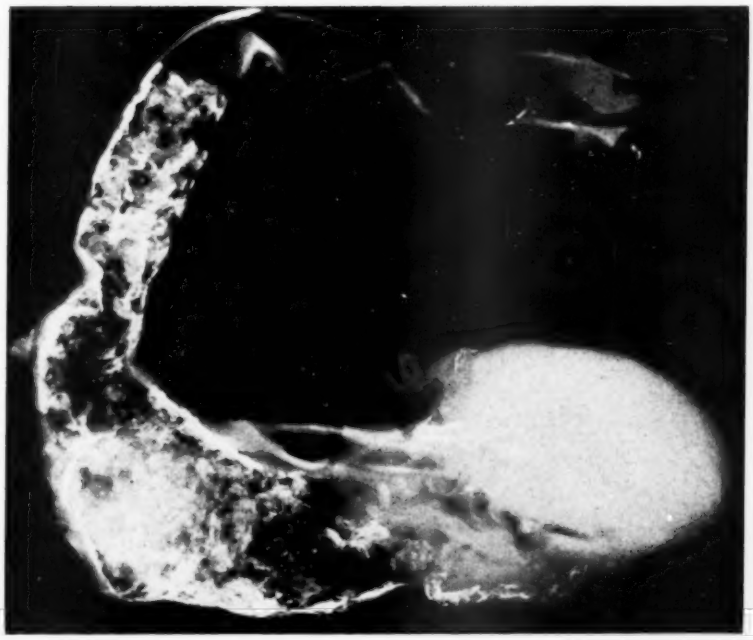

Fig. 2.—Post-mortem x-ray film of aorta shown in Fig. 1.

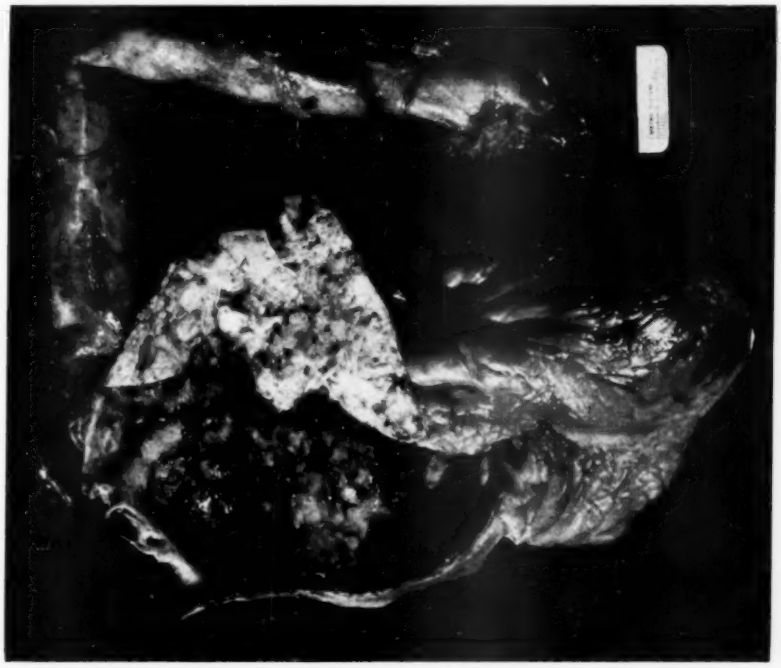

Fig. 1.—Post-mortem specimen of syphilitic aortitis.

Fig. 4.—Post-mortem specimen of atherosclerosis of aorta.

Fig. 3.—Ante-mortem x-ray film of aorta shown in Figs. 1 and 2.

showed several illustrations of roentgenograms which revealed calcification, but except for mentioning the presence of lime salt deposits, he made no statement as to its significance.

The only controlled study found was one made at the Cleveland City Hospital by Jackman and Lubert,[12] who gave comparative figures in sixty-six cases of syphilitic aortitis and sixty-two cases of severe atherosclerosis of the

Fig. 5.—Post-mortem x-ray film of aorta shown in Fig. 4.

thoracic aorta. They found calcification of the ascending aorta in 22.7 per cent of the cases of syphilitic aortitis, as compared with 3.2 per cent of the cases of severe atherosclerosis. They concluded that linear calcification of the ascending aorta is a valuable sign of syphilitic aortitis.

MATERIAL AND OBSERVATIONS

A review was made of all cases of syphilitic aortitis that came to autopsy at the Los Angeles County General Hospital from December, 1938, to July, 1947. Of a total of 400 cases, films of 122 patients with roentgenographic studies prior

to death were available for examination. Eight hundred one autopsied cases of atherosclerosis of the aorta of the same period were studied until 100 cases with available x-ray films were collected. These films were unselected. Routine roentgen techniques were used and many portable bedside films were included. Calcification was declared to be present only in definite cases. All questionable films were read as negative.

Of the 122 cases of syphilitic aortitis, twenty-two (18 per cent) showed calcification of the ascending aorta, as compared with two (2 per cent) of the 100 cases of atherosclerosis of the aorta. These figures are quite similar to those of Jackman and Lubert[12] which have been cited.

The average age of the syphilitic patients showing calcification was 59.5 years, with a range between 43 and 77 years; an average of 54.9 years, with a range of 26 to 82 years, was present in the group which showed no calcification. In the arteriosclerotic series the average age of the patients in whom calcification was present was 83 years, with a range of 81 to 85 years; the average age was 67.3 years, with a range of 36 to 87 years in the patients of the arteriosclerotic series who showed no calcification. These figures are again quite similar to those of the previously reported series[12] in which the syphilitic group showed an average age of 57 years in patients with calcification and 52 years in the patients showing no calcification. The ages of the patients with calcification and arteriosclerosis, however, were considerably higher in the present series, with the average being 83 years, as compared with 62.5 years in the series reported from the Cleveland City Hospital.

In the group exhibiting calcification, men predominated, the proportion being eighteen men to four women in the syphilitic cases, and an equal division between men and women in the atherosclerotic patients. The earlier report showed nine men to six women in the syphilitic group and all men in the arteriosclerotic group.

Color made little difference in the incidence of calcification. Of the total number of cases of syphilitic aortitis, there were twenty-five Negroes (20.4 per cent), with five out of twenty-two (22.7 per cent), showing calcification. These figures again are not significantly different from those of Jackman and Lubert,[12] who reported that 33.3 per cent of the cases of calcification occurred in Negro patients.

Serology positive for syphilis was found in the blood or spinal fluid of sixteen (72.7 per cent) of the twenty-two syphilitic patients with calcification and eighty-six (86 per cent) of the patients without calcification. The report of Jackman and Lubert[12] listed positive serology in 60 per cent of syphilitic patients with calcification and in 78.4 per cent of syphilitic patients without calcification.

The histories of the patients of the syphilitic series were surveyed, and in the group showing calcification, six of the twenty-two patients gave the duration of time from the primary lesion to death. This duration averaged 34.6 years. In the syphilitic patients not showing calcification, the average duration was 27.2 years in sixteen patients in whom the duration could be determined.

The older age levels and the longer duration of the syphilitic process in the group exhibiting calcification, coupled with the lower percentage of positive

serology, confirm the impression that as the duration of the syphilitic process increases, the positive serology tends to diminish, and the atheromatosis with calcification of the ascending aorta increases.

The presence of aortic insufficiency, found either clinically or at necropsy, appears to have no significant relationship to the calcification process. Insufficiency was present in 45.4 per cent of the patients with calcification and in 36 per cent of the syphilitic patients without calcification. This differs considerably from the data given in the Cleveland report in which insufficiency was found in only 13.3 per cent of the patients showing calcification and in 39.2 per cent of the patients in whom no calcification was found.

Tables I and II summarize the findings arrived at by both clinics.

DISCUSSION

The difference in the elective localization of the atheromatosis in the thoracic aorta in syphilis and arteriosclerosis has been demonstrated. As the lesions progress, with the deposition of lime salts in the atheromatous plaques, roentgenographic demonstration of the presence of calcification in the different portions of the aorta should give valuable clues as to the etiology of the underlying processes. It must be emphasized that this is a late sign in syphilitic aortitis and of no value in the early diagnosis, which can only be made by careful and repeated examination of the type of pulsation in the ascending aorta as demonstrated by fluoroscopic examination[13,14] and by application of diagnostic criteria as laid down by Maynard[15] and Woodruff.[16]

Inasmuch as the walls of the aorta are in constant motion, slow exposures used on routine chest films will blur the calcifications and make their detection difficult or impossible. Very rapid exposures (1/20 to 1/30 second), using sufficiently heavy exposure to reveal detail in the cardiomediastinal opacity (usually obtained by high kilovoltage), will detect the lime salt deposits early. In the present series, 20 per cent of the patients in the noncalcific group showed calcification at autopsy which was not detected by the routine film techniques used. In only eight cases of the twenty-two with calcification detected by x-ray was calcification mentioned by the pathologist in the autopsy protocol. In view of these findings, it is felt that a considerably higher incidence of positive roentgenograms can be accomplished by the improved techniques and can be made to approach the figures of 39 to 50 per cent obtained in the clinical cases which prompted this study.

The posteroanterior position will show almost all positive cases, although frequently the left anterior oblique position is more satisfactory. In this view the calcification is present in the ascending aorta 20 to 30 mm. inside the vascular shadow and is seen within the cardiac shadow, starting in the region of the aortic valve. Fig. 6 demonstrates marked calcification of this type, as seen in the left oblique position.

The presence of calcification of the ascending aorta in 18 per cent of the syphilitic cases, as compared with only 2 per cent in the arteriosclerotic series, makes the roentgenographic demonstration of calcification a significant factor in the diagnosis of syphilitic aortitis even with the absence of positive serology,

TABLE I. SUMMARY OF THE FINDINGS ARRIVED AT BY THE CLINICS AT THE LOS ANGELES COUNTY GENERAL HOSPITAL AND THE CLEVELAND CITY HOSPITAL

	NUMBER		AGE		SEX	
	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL
Syphilitic calcific group (Calcification in ascending aorta)	22 or 18%	15 or 22.7%	59.5 average 43–77 range	57 average 32–71 range	18 male 4 female	9 male 6 female
Arteriosclerotic calcific group	2 or 2%	2 or 3.2%	83 average 81–85 range	62.5 average 60–65 range	1 male 1 female	2 male 0 female
Syphilitic noncalcific group	100 or 82%	51 or 77.3%	54.9 average 26–82 range	52 average 35–72 range	79 male 21 female	41 male 10 female
Arteriosclerotic noncalcific group	98 or 98%	60 or 96.8%	67.3 average 36–87 range	70 average 44–92 range	69 male 29 female	36 male 24 female

TABLE II. SUMMARY OF THE FINDINGS ARRIVED AT BY THE CLINICS AT THE LOS ANGELES COUNTY GENERAL HOSPITAL AND THE CLEVELAND CITY HOSPITAL

	COLOR		SEROLOGY		AORTIC INSUFFICIENCY	
	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL	SERIES FROM LOS ANGELES COUNTY GENERAL HOSPITAL	SERIES FROM CLEVELAND CITY HOSPITAL
Syphilitic calcific group (Calcification in ascending aorta)	19 white 5 Negro	10 white 5 Negro	Pos. 16 Neg. 5 Doubt. 1	Pos. 9 Neg. 3 None 3	10 present 12 absent	2 present 13 absent
Arteriosclerotic calcific group	2 white 0 Negro	2 white 0 Negro	Pos. 1 Neg. 1	Pos. 1 Neg. 1	0 present 2 absent	1 present 1 absent
Syphilitic noncalcific group	79 white 21 Negro	24 white 27 Negro	Pos. 86 Neg. 10 Doubt. 3 None 1	Pos. 40 Neg. 9 None 2	36 present 64 absent	20 present 31 absent
Arteriosclerotic noncalcific group	96 white 2 Negro	54 white 6 Negro	Pos. 3 Neg. 88 None 7	Pos. 6 Neg. 54	1 present 97 absent	0 present 60 absent

Fig. 6.—Linear calcification of ascending aorta in syphilitic aortitis as seen in left-oblique position.

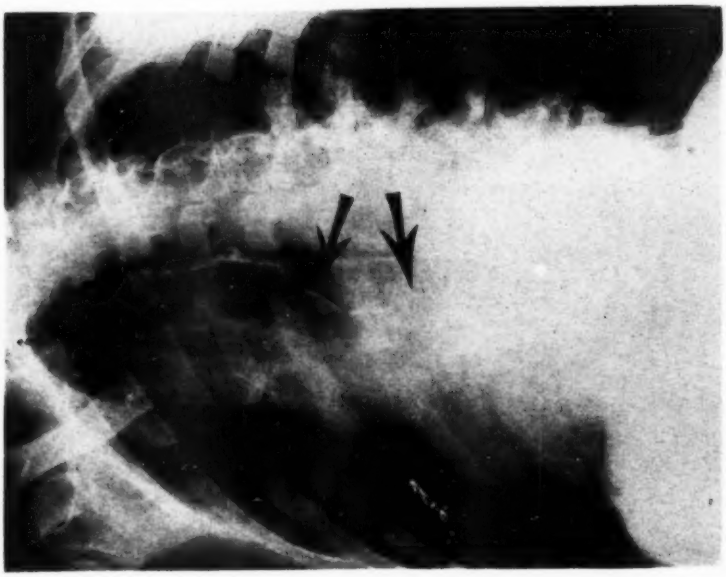

Fig.7.—(H.R. 974-471) Calcification of ascending aorta in syphilitic aortitis.

for it has been demonstrated that as the disease progresses in age, calcification becomes more prominent and the incidence of positive serology decreases.

The youngest patient in the nonsyphilitic groups of both series was a 60-year-old man; the average age was 72.7 years. In the syphilitic group the youngest age represented was 32 years and the average age was 58 years. It must be remembered that syphilis is a disease which is usually acquired early in life, and, therefore, in spite of the fact that the average duration of the disease in patients showing calcification was 34.6 years, calcification is found earlier in life in syphilitic patients, than in the arteriosclerotic group. Demonstrable calcification in patients under 60 years of age is strong evidence that the underlying process is syphilis.

The presence of calcification of the ascending aorta is of value in the differential diagnosis of aortic insufficiency as to rheumatic, syphilitic, or arteriosclerotic etiology. Fig. 7 illustrates a case in point (H. R. 974-471). The patient was a white man, 43 years of age, who entered the hospital in July, 1946. Aortic systolic and diastolic murmurs and a mitral systolic murmur were present. One examiner also heard an apical diastolic rumbling murmur. The patient gave the history of having had syphilis twenty years previously which had been adequately treated. The serology was negative. It was felt that this was a case of combined rheumatic valvular disease until x-ray study revealed calcification of the entire thoracic aorta of marked degree. The patient came to necropsy approximately one year later. There was no evidence of old or recent rheumatic valvulitis. The dilated aorta showed marked scarring typical of syphilis and superimposed atherosclerosis from the aortic ring to the diaphragm.

Calcification of the ascending aorta is also of value in distinguishing thoracic aneurysms from neoplasms. The presence of calcification implies the presence of syphilis which may swing the balance in favor of the diagnosis of syphilitic aneurysm. This is particularly true in the case of aneurysms of the abdominal aorta. It has long been known that most abdominal aneurysms are arteriosclerotic in origin.[17] In the present study 2.2 per cent of the syphilitic patients had abdominal aortic aneurysms (9 in 400 cases), as compared with 4.1 per cent in the arteriosclerotic series (36 in 801 cases). In Fig. 8 is shown the heart and aorta of a patient with an abdominal aneurysm in which calcification of the ascending aorta helped to demonstrate the syphilitic etiology. The patient (P.G. 708-932) was a white man, 53 years of age, admitted to the hospital in August, 1943, with the chief complaint of pain in the lumbar area which had been present for twenty-five years. He developed a penile lesion in 1910 with a positive Wassermann and received antisyphilitic therapy for two years. Another course of treatment of two years' duration was given from 1938 to 1940. Examination revealed an old acid-fast process in the lungs, a blood pressure of 145/90, no cardiac enlargement, and apical and aortic systolic murmurs. X-ray examination of the abdomen showed marked calcification of the abdominal aorta. Marked destruction of the bodies of the first and second lumbar vertebrae was present with curvilinear calcification, 9.0 cm. in diameter, projecting to the left and ventrally from the spine just above the area of vertebral destruction. The diagnoses considered were Pott's disease with old, calcified, soft-tissue abscess

and aneurysm of the abdominal aorta. Examination of the film of the thoracic aorta showed marked calcification. The patient expired suddenly two months after admission. At necropsy the mass proved to be an aneurysm, syphilitic in etiology, which had ruptured into the right thorax and produced death. The thoracic aorta showed dilatation with typical longitudinal wrinkling and atheromatosis with heavy calcification most marked in the ascending and transverse portions.

Fig. 8.—(P.G. 708-932) Calcification of aorta in patient with syphilitic abdominal aneurysm.

SUMMARY

1. The different sites of deposition of calcium in the thoracic aorta in syphilis and arteriosclerosis have been demonstrated.

2. Linear calcification of the ascending aorta in patients under 60 years of age is due to syphilitic aortitis in the large majority of cases.

3. As pointed out by Jackman and Lubert,[12] when calcification in this location is present, it may outweigh the diagnostic implication of a negative serology.

4. Calcification of the ascending aorta is evidence of late, relatively inactive syphilis.

5. Calcification of the ascending aorta is a valuable aid in the differential diagnosis of the etiology of aortic insufficiency and in distinguishing aneurysms from neoplasms.

The authors wish to thank Mr. Lloyd Matlovsky for the technical work in preparing the illustrations.

ADDENDUM

Since this paper was submitted for publication, the study of Leighton (Radiology **51**:257, 1948) has appeared. Of eighteen cases of syphilitic aortitis, proved at autopsy, nine (50 per cent) showed calcification of the ascending aorta. Of thirty-seven clinical cases of syphilitic aortitis studied, seventeen (43 per cent) showed calcification of the ascending aorta.

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BIOMICROSCOPY OF CONJUNCTIVAL VESSELS IN HYPERTENSION

A Capillary "Hypertension Pattern" and the Occurrence of Intravascular Clumping (Sludged Blood) Are Described

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THE role played by capillaries in the hypertension disease process has not been generally emphasized and consequently has received inadequate clinical study and definition. Perhaps one explanation for the failure to evaluate completely the entire vascular tree in hypertension lies in the fact that the investigator has been limited by cumbersome, inadequate methods and an all too frequent lack of appreciation of the importance of the capillary in vascular physiology. From the morphologic approach pathologists have generally failed to recognize variations from normality in hypertension. As a result, the area of vascular pathology associated with hypertension has been rather sharply limited to the more striking arteriolar involvement. It is our purpose to evaluate capillary as well as arteriolar pathology in clinical assays of hypertension.

The older methods of nail-bed capillaroscopy have fallen into disuse because they failed to provide adequate definition of the peripheral vascular components. An excellent review of these techniques for capillary loop visualization was presented by Roth[1] in 1946. The origin of the capillary microscope was attributed to Lombard,[2] 1912, who first visualized the nail-fold capillaries in man. With magnifications up to 75 times, capillaries at the bases of both the finger and toenails were described as distinct comma-shaped loops. In 1917, Weiss and Müller[3] first reported the clinical application of the method and took photomicrographs of the fields visualized. They described the presence of definite deformities and related them to disease entities. In acute nephritis the authors described a generalized widening and an increased number of capillaries, in Raynaud's disease marked irregularities were present, and in arteriosclerosis the capillaries were found to be longer and more tortuous than normal.

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In 1922, Boas,[4] using the Lombard technique, described the nail-fold capillaries in hypertension. From a study based on an undisclosed number of cases, this author concluded "the most that we can say is that in diseases in which the vascular system is affected the capillaries tend to change in appearance, and that this change manifests itself chiefly in an increase in length and tortuosity of the vessels." He also pointed out the difficulties in visualizing capillary flow but described a definite rapid flow in essential hypertension. Brown[5] (1922), using the same method described marked capillary changes in fifty cases of cardiovascular renal disease. The most constant findings were a contracted type of capillary, frequent invisibility of the arterial limb, and marked disturbance in flow. In some areas capillaries appeared elongated and looped. The changes in flow were described as "halting and jerky" and at times isolated capillaries would disappear from view. There are, according to Brown, "essential differences in the capillaries of chronic nephritis and arteriosclerosis with or without hypertension." However, "in patients with malignant hypertension the morphologic and functional changes were most marked."

In 1924, Grzechowiak[6] found changes in the capillaries in hypertension characterized by a beaded type of blood flow and varieties of shapes of loops during the active illness with a return to normal upon the subsidence of symptoms.

Other investigators utilizing the same Lombard technique with various slight improvements failed to confirm the presence of consistent morphologic or functional changes in the peripheral capillary bed in hypertension. Notable among these studies was that reported in 1932 by Mufson,[7] who could not identify such irregularities as Grzechowiak had described. It is interesting to note that Mufson, while concentrating primarily on capillary pressure changes in hypertension, described a frequent narrowing, especially at the arteriole end, and a normal or more rapid flow of blood. Consistent with these findings were those of normal or increased capillary pressure in hypertension.

In an extensive report, Wright and Duryee[8] in 1933 completely failed to confirm the previous reports of capillary changes associated with hypertension per se.

The importance of capillaries in the complete vascular network was being emphasized during this same period. The classical investigations of Cannon[9] on the role of capillary stasis in shock appeared in 1918. Dale[10] described the "paradoxical reaction" of histamine, which increased the tone of arterial muscle but produced a fall in blood pressure on intravenous injection. The explanation for this paradox was found in the capillaries where paralysis, dilatation, and stasis resulted from histamine stimulation. These studies together with the extensive investigations concerning normal capillaries by Krogh[11] and his students (1922-1929) served to establish a sound base line of essential principles and facts.

In 1921 Zeller[12] reported observations on the conjunctival vessels, using a corneal microscope with magnifications of 64 times. He observed normal blood flow and described intravascular as well as capillary abnormalities in arteriosclerosis, syphilis, and diabetes. Miliary aneurysms and corkscrew-type tortuosities were described. Small hemorrhages, passive venous congestion, and variations in flow rates were noted. His series did not include observations on hypertension.

Utilizing recent advances contributed by studies of living circulation in animals (Krogh,[11] Landis,[13] Knisely,[14] Lack[15]), an adaptation of basic techniques has proved useful and easily applicable to the clinical patient.

METHOD

The conjunctival vessels overlying the sclera of the eye were observed by reflecting bright parallel beams of light off the sclera. The images of the conjunctival vascular tree were studied by direct microscopy (Fig. 1). An ophthalmological slit lamp apparatus provided support for the patient's head and a maneuverable light source. A compound microscope was mounted on a horizontal rack

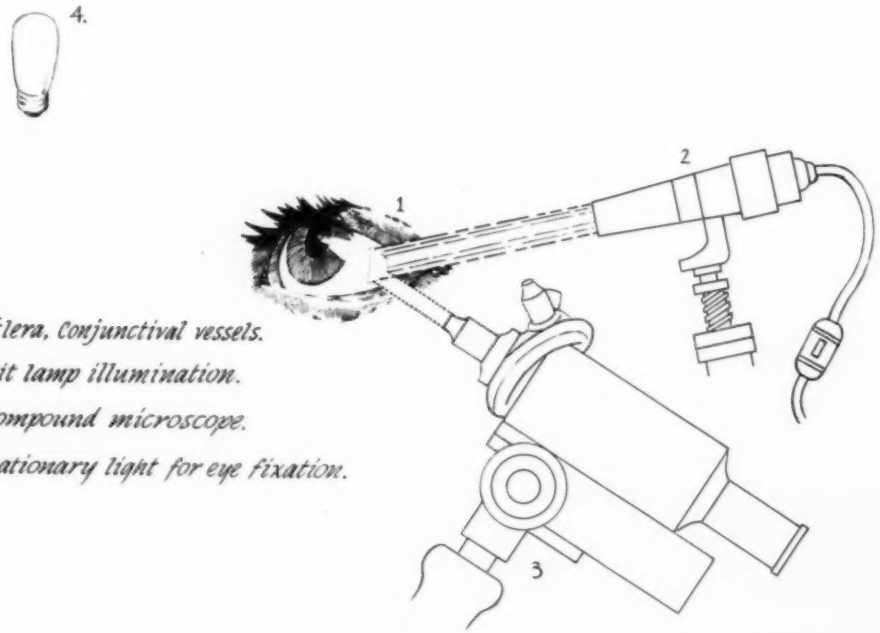
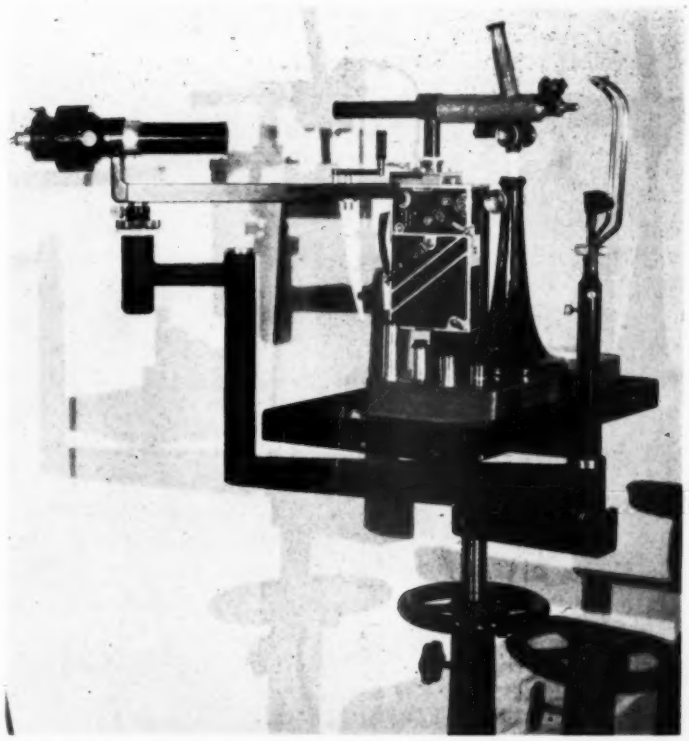


Fig. 1.—Diagram of apparatus for biomicroscopy of bulbar conjunctiva. The compound microscope (*3*) was replaced by a stereoscopic dissection microscope for survey studies.

and pinion; 16 and 24 mm. objectives provided safe working distances (Fig. 2,*A* and *B*). Wide-field oculars, 3 × to 20 ×, gave sufficient definition and magnification for these studies. Most observations were made with a 16 mm. apochromatic objective (for use without coverglass) and 5 or 10 × wide-field oculars. As much of the white of the eye as possible was exposed by the patient's fixation on a strategically placed small, red light in a darkened examination room. This technique was used for both compound and stereoscope microscopy. A wide-field stereoscopic dissecting microscope (Spencer) mounted on a side arm was used alternately with the rebuilt compound microscope described. The stereoscopic microscope was excellent for survey work and intravascular studies. Complete arteriovenous patterns with capillary networks were clearly visualized.



A.

B.

Fig. 2.—*A*, Photograph of apparatus showing side arm ocular mounting of camera. *B*, Close-up of apparatus with subject in position. Slit lamp illumination of the sclera was adequate for routine use.

Repeated examinations of patients made it possible to study changes in the peripheral vessels. Permanent records were obtained by Kodachrome cinematography, drawings from which are presented. The present apparatus is adapted for cinematography with an Eastman 16 mm. Ciné-Kodak Special Camera, mounted on the microscope by a side arm ocular. This ocular permits simultaneous recording and direct observation for continuous focusing.

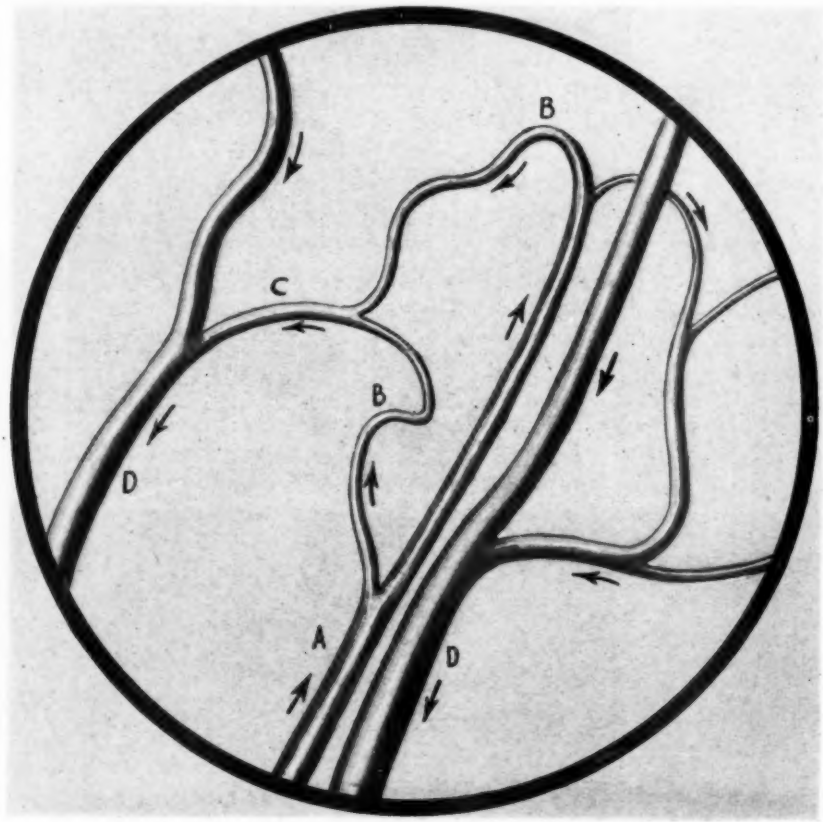


Fig. 3.—Normal capillary pattern of conjunctiva. Arteriole and capillaries are uniform with smooth parallel walls. *A*, arteriole; *B*, capillaries; *C*, venule; *D*, collecting vein. Approximately × 100 (on film).

RESULTS

Normotensive Subjects.—Two control series were concurrently studied. One, a hospital group of sixty-four normotensive patients, and, two, a group of fifty normal adults. Fig. 3 presents the structural plan of a typical normotensive subject (R.J.). The arterioles divide into numerous side capillaries and terminate with an end capillary. The latter, on occasion, functions as a "through and through" channel. The capillaries appear to be of uniform caliber throughout with a smooth, winding course and no evidence of sacculations or abnormal points of constriction. The capillary of the bulbar conjunctiva has indefinite

subdivisions of postarterial, midloop, and prevenule segments. Only rare arteriovenous anastomoses of the short type are seen. There are individual variations in venous patterns with frequent tortuosities, varying with individuals and being correlated in some degree with the age of the patient. Flow rates in normal individuals are not remarkable and are consistent with the physiology of a given area. With magnifications of one hundred times or more, it is possible to trace the course of an individual red cell through the entire capillary loop.

The morphologic changes in the two control series will be briefly summarized. Of the sixty-four nonhypertensive hospital patients, capillary changes were absent in forty-six (72 per cent) and present in eighteen (28 per cent). The changes noted were only minimal. No patients revealed abnormalities of the hypertension pattern, but showed, on the other hand, various changes such as abnormal dilatations, minimal narrowing, spiderweb branches, and a rare focal nodularity. In the fifty normal adults of the control series the capillaries were normal in appearance in all instances. Capillary distensibility was present throughout and there was no evidence of thickening of the capillary wall.

Hypertensive Subjects.—A series of one hundred hypertension patients with blood pressures of 150/100 or more were evaluated by biomicroscopy. Definite capillary irregularities were present in ninety-eight of the patients. These have been roughly evaluated as being of minimal involvement in 9 per cent, moderate in 57 per cent, and marked in 34 per cent. These changes were morphologic, consisting of generalized narrowing of the capillary lumen, elongation with angular tortuosities, abnormal loopings, focal constrictions, and occasional sacculations.

Definite angularities (that is, fixed turns of roughly 30 degrees or more), and an increased length of over-all capillary segment with abnormal loopings were consistent findings. Accompanying such morphologic changes was increased thickness of capillary wall which showed some degree of thickening in 83 per cent. In striking correlation with the morphologic irregularities was the loss of normal capillary distensibility in 89 per cent.

Marked sparseness of the capillary bed was found in cases of long-standing hypertension. The typical capillary findings in hypertension are shown (Fig. 4) in a drawing copied from a 16 mm. Kodachrome moving picture of the patient. The elongation of individual capillaries with a tendency to looping of the midcapillary segment appeared as a striking early change. The thick-walled capillaries seen in hypertension have a tubular appearance, and fixed tortuosities are striking. The loss of normal distensibility was easily noted when large intravascular red cell clumps and thrombi could be followed through capillary channels. Such findings were sufficiently striking and consistent to suggest a hypertension pattern of capillary pathology as represented diagrammatically in Fig. 5.

The capillary changes of the "hypertension type" and the height of the diastolic pressures showed a definite correlation. With increasing diastolic pressures there was a greater incidence of marked capillary change. In the two patients in whom capillary findings were absent the diastolic pressures occurred in the 100 to 119 mm. group; both of these patients had histories of early hypertension.

The age distribution curve reveals a wide sampling with predominance of patients in the middle age groups. There was no correlation between the age of an individual patient and the degree of capillary changes of the hypertension type described.

Sex distribution of this hypertension series bears no significant relationship to the degree of capillary pathology observed.

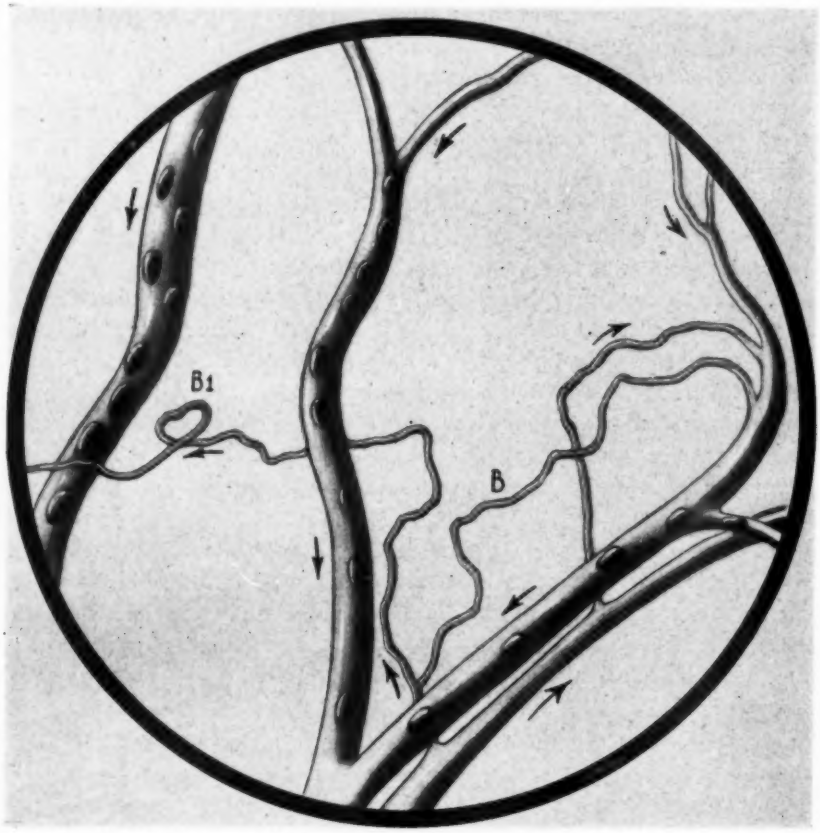


Fig. 4.—Capillaries of conjunctiva in hypertension. Traced from 16 mm. Kodachrome film of patient. Note elongated, narrowed capillaries (*B*) with marked tortuosities and sharp, fixed angular turns. Capillary loop shown (*B*[1]). Approximately × 100 (on film).

The evaluation of arterioles in the hypertension patients revealed definite irregularities in 80 per cent, with an entirely normal arteriolar structure present in 10 per cent. There was no evaluation made in the remaining 10 per cent.

INTRAVASCULAR AGGLUTINATION PHENOMENON OR "SLUDGED BLOOD"

The fact that intravascular pathology of considerable severity involving clumped masses of red cells and/or clumped masses of white blood cells may be present in numerous disease states has been reported by several early investigators. In 1908, Cropper[16] described the intravascular clumping of infected red

cells in a fatal case of pernicious malaria. He suggested that such formations might form embolisms, thromboses, or infarctions in various organs. Iwai and Meisai,[17] 1925, reported the formation of agglutinated masses of red cells in Raynaud's disease. At their invitation Hayano, using a Zeiss corneal microscope, observed changes in the flow of conjunctival vessels. Broken columns of blood flow in capillaries were described after bathing with cold water and it was felt that these could be due to the formation of small, intravascular blood clots.

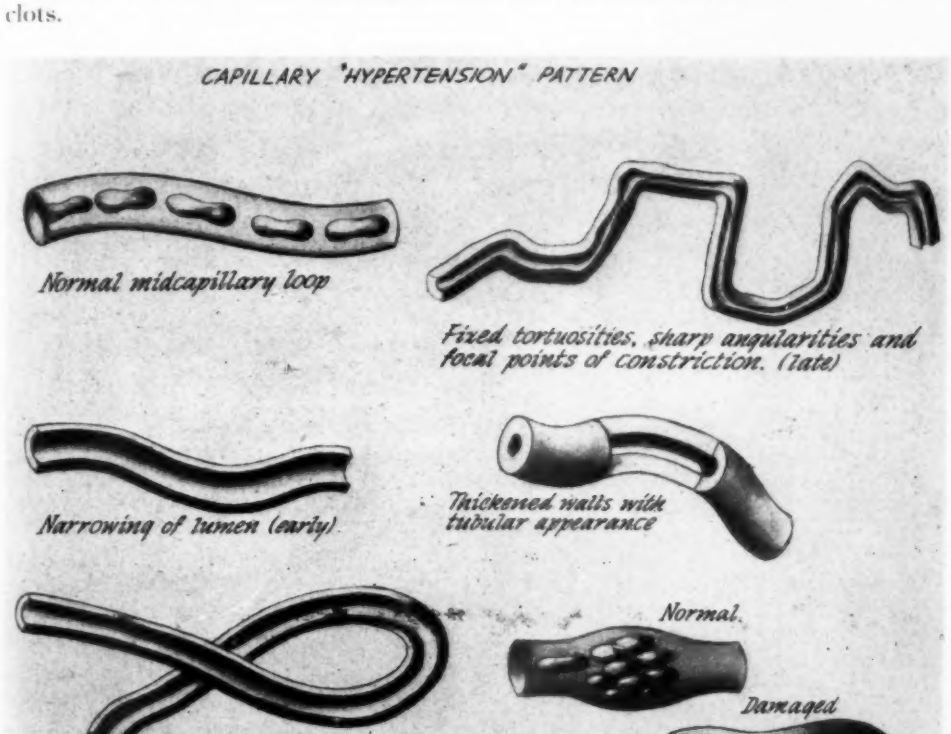


Fig. 5.—Hypertension pattern of capillary changes as seen with the biomicroscope (diagrammatic). The significant morphologic changes in conjunctival vessels were confirmed by histopathologic study of necropsy material.

Histologically, intravascular agglutinated masses of red cells in malaria were demonstrated in various tissues at autopsy by Dudgeon and Clarke[18] in 1917. Thromboses were particularly prominent in the adrenals, brain, and kidneys. They pointed out that this observation of agglutinated erythrocytes in malaria leads not only to the occlusion of capillaries but to obstruction of arterioles as well.

This phenomenon consists primarily of intravascular clumpings of red cells forming large, agglutinated, firm masses inconsistent with shell layer type of normal vascular flow. It appeared to us that such intravascular changes were interesting but definitely nonspecific. Although these changes were of un-

doubted importance in vascular pathology, it was not within the province of this paper to embark upon a study of this abnormality. However, we noted that intravascular agglutinations of some severity were present in many of our subjects. These changes were graded roughly on a basis of size, number, and toughness of clumps (Fig. 6). Grade 1 represented fine granularities of several erythrocytes which are rather uniform and not too upsetting to flow rates; Grade 2 indicated definite clumping which tends to hold together in larger collecting veins; Grade 3 indicated large agglutinations which completely block out normal flow; and Grade 4 represented almost complete clumping of erythrocytes, which suggests the appearance of "sludge."

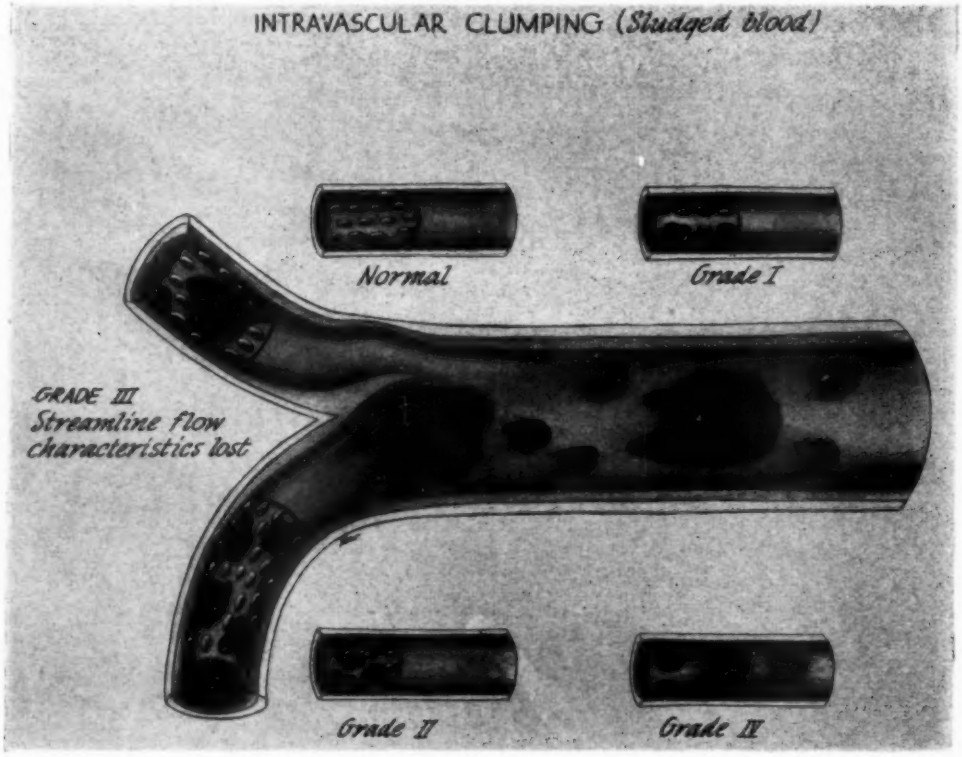


Fig. 6.—Grading of severity of intravascular red cell clumpings or sludged blood. The clinical significance of these various grades has not yet been established.

Of our series of hypertension patients, intravascular agglutinations of erythrocytes were absent in only four. Subjective estimations revealed 50 per cent with Grade 1 clumping, 45 per cent with Grade 2, 4 per cent with Grade 3, and 1 per cent with Grade 4 clumping. A sharp line of demarcation occurred in the hypertension series between Grades 2 and 3, with 95 per cent having involvement in Grades 1 and 2 indicative of minimal to moderate severity. There was no relation of degree of clumping to blood pressure levels. Transient capillary and venous thromboses were present in 73 per cent of the hypertension series.

Of the sixty-four nonhypertensive hospital control patients, intravascular agglutinations were present in forty-three, with fourteen in Grade 1, twenty-three in Grade 2, five in Grade 3, and one in Grade 4. Of the fifty normal adult control subjects, only one showed intravascular pathology (Grade 1). It was of interest to note that the presence of granularities in this one subject may be related to the fact that this individual was recuperating from an upper respiratory infection.

DISCUSSION

The original premise for studying patients by direct visualization of the conjunctival vessels was directed toward analyses of intravascular pathology similar to the recently described "sludged blood" by Knisely and co-workers[19] at the University of Chicago and the University of Tennessee. The intravascular clumping of red cells is an important physical phenomenon and is definitely inconsistent with "streamlined" hemodynamics. Altered cell nutrition as a result of inadequate flow characteristics and the formation of thromboses and infarctions subsequent to such intravascular clumping may all be of considerable significance in the explanation of numerous disease manifestations. However, the nonspecificity of this phenomenon immediately became apparent and its relation to any given disease process required additional clarification and definition of basic factors involved. On the other hand, the adaptability of this technique toward an analysis of the morphologic pathology of the peripheral vascular tree in various disease states, and hypertension in particular, soon became evident.

An advantage of the method presented lies in the fact that the wall of individual capillaries can be discerned with proper illumination and magnification. The clear images obtained contrast sharply with the older methods and make possible more critical analyses of peripheral vascular pathology.

The consistent changes in capillaries associated with hypertension indicate that the area of peripheral vascular resistance includes capillaries as well as arterioles. On occasion, significant findings in hypertension have been confined to the capillaries. The arterioles of the conjunctiva showed no changes in these cases. If this peripheral area were indicative of general systemic involvement, it would suggest that peripheral resistance could be initiated by capillaries in some cases. Similar capillary pathology in hypertension was reported in the central nervous system by Scheinker,[20] in 1948. He demonstrated at necropsy that vascular alterations in early arterial hypertension were confined mostly to capillaries with evidence of proliferative and degenerative changes. Such changes in capillaries may be correlated with a general vascular deterioration, and progressive atresia of individual capillaries might well occur.

SUMMARY AND CONCLUSIONS

1. A new method of biomicroscopy of conjunctival vessels, utilizing high magnification (up to 200 times), is presented.

2. The results from a study of one hundred cases of hypertension suggest a "hypertension pattern" of capillary pathology. This pattern is characterized

by extensive narrowing, elongation, and looping of capillaries, which, in addition, show fixed angularities or tortuosities, tubular thickening of walls, and loss of normal distensibility. Ninety-eight per cent of all hypertensive patients showed significant capillary changes of this type.

3. The severity of this capillary hypertension pattern correlates directly with the rise in diastolic pressure.

4. No significant correlations of capillary vascular damage with sex or age could be determined.

5. Arteriolar pathology is noted in 80 per cent of the hypertension series.

6. Nonhypertensive hospital patients, who composed a control series, showed no capillary involvement in 72 per cent. Minimal changes of bizarre types were present in 28 per cent; none showed the "hypertension pattern" of capillary pathology.

7. Intravascular clumping of red cells was noted in 96 per cent of the hypertension series and in 67 per cent of the control series.

8. The findings of this study indicate that it may be worth while clinically to evaluate the role of the capillary in hypertension by this method and to direct efforts toward a systemic evaluation of the pathology of the capillary tree as it relates to the hypertension process.

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THE NORMAL UNIPOLAR PRECORDIAL AND LIMB LEAD ELECTROCARDIOGRAM

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THE increasing recognition of the diagnostic value of unipolar precordial and limb leads has given a tremendous impetus to electrocardiography. A number of publications have described various phases of unipolar precordial electrocardiography and the evaluation of patterns such as those seen in myocardial infarction, bundle branch block, and ventricular hypertrophy.[1-11] However, statistical data on the normal electrocardiogram as obtained by unipolar extremity and precordial leads are extremely scant. The publication to which most authors refer is that of Kossmann and Johnston,[12] but the data of these authors are based on only thirty cases, in which V_6 was not used. Since their paper in 1935, other articles limited to certain phases of the normal precordial electrocardiogram have appeared, such as data for children[13] and the intrinsic deflection.[14] It was, therefore, felt desirable to study a larger group of normal individuals of various ages, in an attempt to establish more definitely the normal variations. Since this study was completed, two publications on unipolar leads in normal subjects have appeared.[15,16]

Wilson and his co-workers[1] demonstrated in a series of papers that precordial leads may, for practical purposes, be considered semidirect leads from the heart. These workers showed that a close relationship exists between the electrocardiographic pattern obtained from the epicardium of the right ventricle and that obtained from the right precordium, and that a similar relationship exists between patterns obtained from the left ventricle and the left precordium. The value of multiple, as compared to single, precordial leads was stressed by the observation that a precordial or an epicardial electrode largely reflects the potential variations of the myocardium directly under the electrode, and that the effects of distant ventricular areas vary inversely as the cube of the distance.[1] In using multiple precordial leads, the use of an indifferent electrode with potential as near zero as possible is to be preferred. Wilson and his group demonstrated that their central terminal was nearly zero, having a potential of approximately 0.3 millivolt. This is in contrast to the CF leads when the left leg lead may be far from indifferent, especially in vertical hearts.

From the Division of Medicine of the University of California Medical School, San Francisco. Aided in part by a grant from the Mrs. Albert E. Schwabacher Fund.

Furthermore, the recording of unipolar extremity leads requires the use of the central terminal. Goldberger[17] has modified Wilson's technique for taking the unipolar extremity leads, and records "augmented" potentials which are 50 per cent greater than those obtained by the Wilson method. Unipolar precordial leads and unipolar augmented extremity leads have therefore become widely used in electrocardiography.

Since the original work of Lewis,[18] the importance of the intrinsic deflection has been stressed by Wilson and his associates[1] and by Sodi-Pallares and his associates.[14] The time of onset of the beginning of the final downstroke of the QRS complex in relation to the time of onset of the beginning of the QRS complex is said to indicate the time required for the passage of the impulse to the epicardium underlying the exploring electrode. As such, the time of onset of the intrinsic deflection (the ventricular activation time) will be delayed in conditions that increase the mass of myocardium (hypertrophy) or delay the passage of the impulse (bundle branch block or myocardial infarction).

THE ELECTROCARDIOGRAPHIC POSITION OF THE HEART

Wilson and associates[1] have emphasized the importance of the electrocardiographic position of the heart in explaining variations in the electrical axis and patterns in the standard limb leads. These authors have noted that despite similar precordial patterns, some individuals show strikingly different patterns in their standard limb leads and may show left axis deviation, right axis deviation, or no axis deviation. They demonstrated that this variation in the standard leads can be explained by the electrocardiographic position of the heart and its relation to the extremities. The position of the heart may be determined by a comparison of the potential variations of the left arm and left leg leads with those of V_1 and V_6 in the precordial leads. Depending on whether the potential of the left ventricle (V_5 or V_6) is transmitted to the left arm or left leg, Wilson and associates have classified their cases as horizontal or vertical, respectively, referring to the electrocardiographic rather than to the anatomic position of the heart.

SUBJECTS AND METHODS

All the subjects on which the present data are based have had complete physical examinations and six-meter roentgenographic studies of the heart, and, as far as could be determined, were free of cardiovascular disease. None had cardiovascular symptoms or a disease known to affect the heart, such as disease of the thyroid, anemia, rheumatic fever, and so forth. Many were medical students and members of the house staff. Those composing the group in the third to seventh decades were obtained from flying personnel of the United Air Lines,* whose physical examinations and requirements for performance are notably high; and from psychiatric patients in the Langley Porter Clinic* who were studied prior to electric shock treatment. None of

*The authors are indebted to Dr. A. C. Ladd, Medical Director, United Air Lines, South San Francisco, Calif., and the Staff at the Langley Porter Clinic, San Francisco, Calif., for their cooperation in this study.

the latter group had cardiovascular disease, as far as could be determined, and had been referred to the clinic solely for their psychiatric disorders. Miscellaneous individuals from all age groups for whom an electrocardiogram had been requested as part of a routine physical examination were included. These individuals had no signs or symptoms of cardiovascular disease. The small group of infants was obtained from the Well-Baby Clinic of the University of California Clinics. Prior to the final statistical evaluation, all the case histories were carefully rescrutinized and any questionably normal subjects were excluded.

One hundred fifty individuals remained, and these were studied with standard limb leads, unipolar precordial leads, and unipolar leads of the left arm (aV_L), right arm (aV_R), and left leg (aV_F). Goldberger's modification of Wilson's[17] method was used. A minimum of six unipolar precordial leads were taken on each case, V_1 to V_6, according to the recommendations of the American Heart Association. The tracings were carefully analyzed and work-sheets were made out recording the amplitude and duration of each significant electrocardiographic variable. In addition, the time of onset of the intrinsic deflection in relation to the onset of the QRS (the ventricular activation time), the electrocardiographic position of the heart, the R/S and R/T ratios, as well as other ratios and factors of voltage were studied.

The age range of the subjects was as follows:

1 to 9 years	5
10 to 19 years	4
20 to 29 years	49
30 to 39 years	45
40 to 49 years	30
50 to 59 years	12
60 years or more	5
	150

RESULTS

The Normal Electrocardiogram.—Table I summarizes the findings in our total series of 150 subjects and includes the total normal group and separate data for those individuals among the normal group who had left or right axis deviation. These data for voltage of the unipolar extremity leads must be decreased by 50 per cent if a direct comparison with the results of Kossmann and Johnston is desired (see above). For example, the mean R wave in V_L in Kossmann and Johnston's[12] data is 1.13 mm.; in our data the corresponding figure for aV_L is 2.1 millimeters.

Electrocardiographic Position of the Heart.—Table II tabulates the electrocardiographic position of the heart obtained in our normal subjects. It was found that there was a direct relationship between left axis deviation in the

TABLE I. THE VENTRICULAR DEFLECTIONS IN THE UNIPOLAR LIMB AND PRECORDIAL LEADS IN NORMAL SUBJECTS (MEASUREMENTS IN MILLIMETERS)

LEAD	NORMAL (150 CASES)			NORMAL—LEFT AXIS DEVIATION (21 CASES)			NORMAL—RIGHT AXIS DEVIATION (19 CASES)		
	MEAN	± ST. DEV.	MIN. MAX.	MEAN	± ST. DEV.	MIN. MAX.	MEAN	± ST. DEV.	MIN. MAX.
V_1									
Q	0	0	(0)	0	0	(0)	0	0	(0)
R	2.3	1.5	(0 7.0)	1.8	1.3	(0 4.5)	2.1	1.6	(0 7.0)
S	8.6	4.3	(2.0 25.0)	8.0	3.7	(3.5 18.0)	8.4	4.3	(1.5 17.0)
T	0.15	1.58	(−0.4 +4.0)	−0.4	1.32	(−2.5 +3.0)	+0.26	1.06	(−1.5 +3.0)
ID	0.02	0.007	(0 0.03)	0.02	0.006	(0 0.02)	0.02	0.008	(0 0.03)
V_2									
Q	0	0	(0)	0	0	(0)	0	0	(0)
R	5.9	3.1	(0 16.0)	5.0	2.9	(2.0 12.0)	5.9	2.8	(2.0 11.0)
S	12.7	5.3	(0 29.0)	10.3	4.8	(4.0 18.0)	15.4	5.0	(4.0 29.0)
T	5.52	3.32	(−3.0 +18.0)	4.08	2.68	(−2.5 +9.0)	4.6	2.34	(+1.5 +11.0)
ID	0.025	0.006	(0 0.04)	0.03	0.006	(0.01 0.035)	0.024	0.008	(0.015 0.04)
V_3									
Q	0.01	0.06	(0 0.5)	0	0	(0)	0	0	(0)
R	8.9	4.3	(1.5 26.0)	8.6	4.0	(4 17.0)	7.4	2.6	(3.0 13.0)
S	8.8	5.3	(0 25.0)	7.5	4.3	(3 16.0)	11.3	5.7	(2.0 25.0)
T	5.38	2.96	(−2.0 +16.0)	4.67	4.37	(−0.1 +13.0)	5.18	2.21	(+2.0 +10.0)
ID	0.03	0.007	(0.02 0.04)	0.03	0.005	(0.02 0.04)	0.029	0.007	(0.015 0.04)
V_4									
Q	0.1	0.4	(0 3.0)	0.05	0.16	(0 0.5)	0.03	0.02	(0 0.5)
R	14.2	5.5	(4.0 27.0)	12.5	5.0	(5.0 27.0)	13.4	4.4	(4.0 23.0)
S	5.2	4.0	(0 20.0)	4.3	3.2	(0 13.0)	6.5	5.0	(0 19.0)
T	4.8	2.76	(0 +17.0)	4.2	2.67	(−0.1 +13.0)	4.18	1.79	(+1.0 +8.0)
ID	0.034	0.007	(0.02 0.05)	0.04	0.007	(0.03 0.045)	0.032	0.007	(0.020.04)

V_5	Q	0.3	0.6	(0	3.0)	0.3	0.4	(0	1.0)	0.2	0.1	(0	1.0)
	R	12.1	4.4	(4.0	24.0)	11.8	5.4	(6.0	24.0)	10.2	3.7	(4.0	20.0)
	S	1.5	1.5	(0	6.0)	1.2	1.1	(0	4.0)	2.0	1.8	(0	6.0)
	T	3.43	1.62	(0	+9.0)	3.45	1.66	(+1.0	+9.0)	3.29	1.49	(+2.0	+8.0)
	ID	0.04	0.01	(0	0.05)	0.04	0.007	(0.025	0.05)	0.033	0.008	(0.02	0.04)
V_6	Q	0.4	0.5	(0	2.0)	0.4	0.4	(0	1.0)	0.3	0.2	(0	2.0)
	R	9.2	3.6	(4.0	22.0)	8.9	4.1	(4.0	19.0)	8.1	3.6	(2.5	16.0)
	S	0.6	1.0	(0	7.0)	0.2	0.5	(0	1.5)	0.8	0.9	(0	3.5)
	T	2.43	1.11	(−0.5	+5.0)	2.4	1.18	(+0.5	+6.0)	2.37	1.01	(+1.5	+5.0)
	ID	0.04	0.01	(0.02	0.05)	0.04	0.01	(0.03	0.05)	0.03	0.01	(0.02	0.05)
V_L	Q	0.2	0.5	(0	3.5)	0.5	0.4	(0	1.0)	0.1	0.2	(0	3.5)
	R	2.1	2.1	(0	10.0)	4.6	2.5	(0.5	10.0)	0.9	0.8	(0	3.0)
	S	0.4	3.9	(0	18.0)	0.3	0.7	(0	3.0)	0.5	3.6	(0	18.0)
	T	0.53	1.26	(−4.0	+6.0)	1.0	0.81	(−1.0	+2.5)	0.45	1.0	(2.0	+2.0)
V_R	Q	2.0	3.7	(0	8.0)	1.0	2.6	(0	6.0)	1.8	2.7	(0	8.0)
	R	0.8	0.9	(0	5.0)	0.4	0.6	(0	1.5)	0.8	0.8	(0	3.5)
	S	4.3	4.0	(0	13.0)	4.3	0.9	(0	8.0)	4.3	4.6	(0	13.0)
	T	−2.31	0.92	(−5.0	+1.5)	2.2	0.67	(−3.0	+1.0)	−2.08	0.84	(−4.0	−1.0)
V_F	Q	0.5	1.4	(0	3.0)	0.4	1.0	(0	5.0)	0.7	0.2	(0	2.0)
	R	1.3	8.3	(0	20.0)	2.7	2.2	(0	8.0)	10.5	4.2	(0.7	20.0)
	S	0.2	1.3	(0	8.0)	1.6	1.4	(0	4.0)	0.4	2.1	(0	2.0)
	T	1.86	1.1	(−0.5	+5.0)	1.4	0.92	(−0.5	+3.0)	1.84	0.96	(+0.5	+4.0)

1.0 = time of onset of the intrinsic deflection or ventricular activation time.

standard leads and horizontal hearts and between right axis deviation and vertical hearts. Records with no axis deviation were intermediate in position (Fig. 1). It was apparent from Table II that the majority of the normal subjects had vertical or semivertical hearts from an electrocardiographic (not anatomic) standpoint.

TABLE II. THE ELECTROCARDIOGRAPHIC POSITION OF THE HEART AS OBTAINED IN 150 NORMAL SUBJECTS

Horizontal	3
Semihorizontal	11
Intermediate	28
Semivertical	68
Vertical	40
	150

Of the fourteen subjects with semihorizontal or horizontal hearts, only two were under the age of 39. This is of some significance, because unless gross obesity or an elevated diaphragm was present (such as occurs in late pregnancy), horizontal hearts were not seen in normal individuals before the fourth decade. The prediction of the electrocardiographic position of the heart from the build of the patient was fairly reliable in slender individuals (who usually had vertical hearts), but one was often surprised to find vertical or intermediate hearts in individuals who were sthenic in appearance and definitely overweight (Fig. 2*A*). In order to determine the effects of position of the heart and axis deviation on the unipolar patterns, data were obtained from nineteen normal subjects whose electrical axes were +80° or more (obtained by the method of Carter and his associates[19]) and from twenty-one normal individuals whose electrical axes were +10° or less (Table I).

The tables and Fig. 1 illustrate that although the precordial leads were essentially similar, the unipolar limb Leads aV_L and aV_F differed in the group with left axis deviation from those in the group with right axis deviation. Lead aV_R was similar in both groups, because in this lead the exploring electrode on the right arm faced the orifices of the great vessels and the cavities of the heart and hence was essentially negative throughout the QRS interval. Since the changes in the unipolar extremity leads were so obviously related to the position of the heart, whereas the precordial leads were much less influenced by the position of the heart, greater reliance must be placed on the precordial leads for electrocardiographic diagnosis. Unusual rotation may explain a variety of so-called atypical electrocardiographic patterns (see Discussion).

The P Wave.—The shape, amplitude, and duration of the P wave did not differ from that noted by previous authors in the standard leads. Almost invariably the P wave was inverted in Lead aV_R, often was inverted in aV_L, and usually was upright in aV_F. The P wave was small and diphasic in a small percentage of normal subjects in V_1, but the broad, negative diphasic quality noted by Hecht[20] in mitral stenosis. and characteristic of auricular enlargement, was not seen. The P wave was usually small and upright or isoelectric in the remaining precordial leads, very rarely diphasic in the left precordial leads.

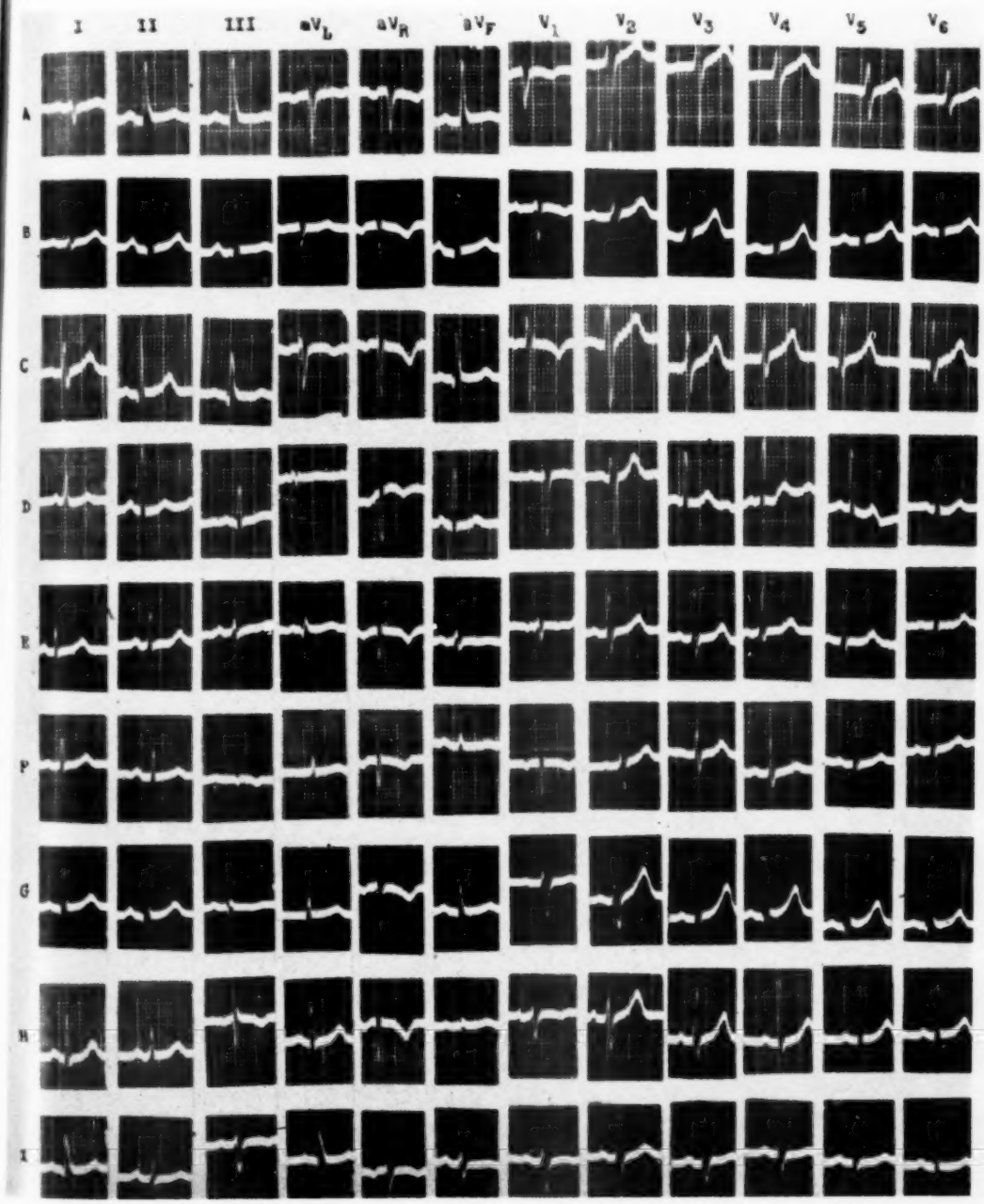

Fig. 1.—Unipolar leads in nine normal subjects arranged in order from the most vertical to the most horizontal positions of the heart.

The QRS Complex.—Fig. 1 illustrates the reciprocal relationship between the R and S waves as the exploring electrode was moved across the precordium from right to left (V_1 to V_6). The R wave usually was small in Leads V_1, V_2, and V_3; became larger in V_4; and obtained its maximum height in either Lead V_4 or V_5, after which it tapered off in V_6 and V_7. The S wave showed a reciprocal decrease, although the decrease in size was more gradual and the change to the left of the transitional zone was not so marked as occurred occasionally with the R wave. The R/S ratio was calculated, and the increase was striking as one moved from the right to the left precordium (Table III*A*).

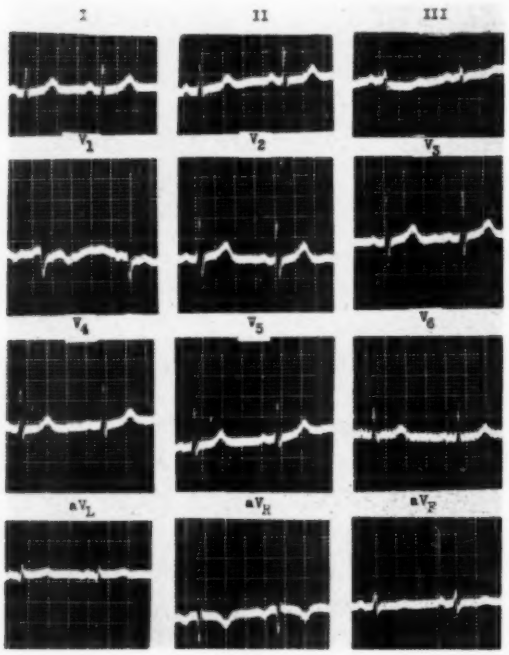

Fig. 2*A*.

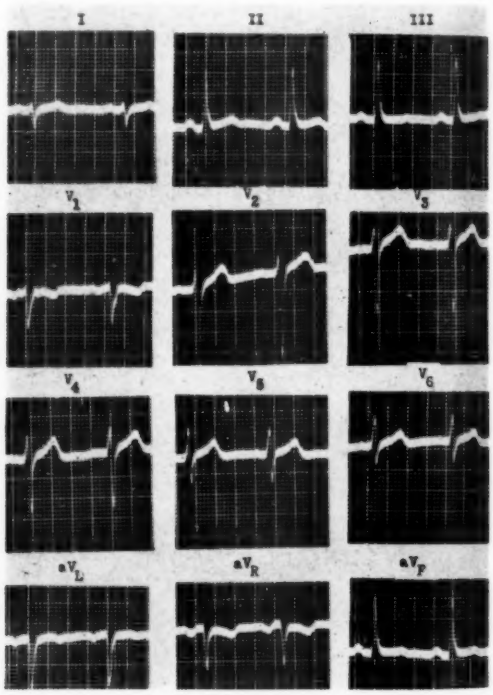

Fig. 2*B*.

Fig. 2 *A*.—A. R., woman, age 48. Obese; 159 pounds, 5 feet 3 inches. Transitional zone between precordial Positions 1 and 2. Note Q wave in aV_L with small total QRS complex.

Fig. 2 *B*.—A. M., man, age 25. Vertical position, axis +105 degrees. Note the relatively low T in aV_F and the inverted T in aV_L. Transitional zone between Positions 5 and 6.

The maximum figure for the R/S ratio in Lead V_1 in the adults was 1.0 and the minimum figure in Lead V_5 was 1.0. The ratio obtained by dividing the R/S ratio in V_5 by the R/S ratio in $V_1 \left(\frac{\text{R/S in } V_5}{\text{R/S in } V_1} \right)$ is noted in Table III*B*.

The transitional zone denoting the change in potential over the right and left ventricles usually occurred in Lead V_3 or V_4, but occasionally was seen in V_2 or V_5 and rarely in V_6 or V_7 (Figs. 2*A* and 2*B*). Notching and slurring of the QRS complex was not uncommon in the complexes obtained from the transitional zone; this was considered to be due to an overlapping of the effects of both ventricles, a normal phenomenon.

TABLE III, A. THE RATIO OF THE R WAVE TO THE S WAVE (R/S RATIO) IN THE PRECORDIAL LEADS OF NORMAL ADULT SUBJECTS

LEAD	MEAN	±ST. DEV.	MIN.	MAX.
V_1	0.3	0.3	(0	1.0)
V_2	0.2	1.2	(0.1	13.0)
V_3	1.4	1.4	(0.1	10.0)
V_4	4.1	3.8	(0.2	19.0)
V_5	7.3	4.7	(1.0	24.0)
V_6	9.0	5.0	(2.3	22.0)

TABLE III, B. THE DATA OBTAINED BY DIVIDING THE R/S RATIO IN V_5 BY THE R/S RATIO IN V_1 $\left(\frac{\text{R/S IN } V_5}{\text{R/S IN } V_1}\right)$ IN NORMAL SUBJECTS

	MEAN	±ST. DEV.	MIN.	MAX.
$\frac{\text{R/S in } V_5}{\text{R/S in } V_1}$	32.0	26.9	(3.6	100)

Voltage of the QRS Complex.—Because of the abnormalities found in the R/S ratio in Leads V_1 and V_5 in ventricular hypertrophy,[9,10] particular attention was paid to the voltage of the various waves of the QRS complex, and the data obtained are summarized in Table I. Data for children are incomplete in view of the frequent presence of high voltage of the QRS complex in normal children. The R/S ratio as obtained from leads over the right and left precordium reflects the relative effects of the right and left ventricles. In addition to the individual voltage of the waves, the total voltage of the left and right ventricular potentials was determined. The sum of R in V_1 and S in V_5 was considered to reflect the total right ventricular potentials; the sum of R in V_5 and S in V_1, the left ventricular potentials. These data were important in providing base-line figures for the diagnosis of ventricular hypertrophy.[9,10] Tables IV and V summarize the findings of these R and S relationships as obtained in Leads V_1 to V_6, in adults (over the age of 20).

TABLE IV. THE SUM OF THE AMPLITUDES OF THE R WAVE IN V_1 AND OF THE S WAVE IN V_5 IN NORMAL ADULT SUBJECTS

	MEAN	±ST. DEV.	MIN.	MAX.
R in V_1 + S in V_5	3.7	2.39	(0	10.5)

TABLE V. THE SUM OF THE AMPLITUDES OF THE S WAVE IN V_1 AND OF THE R WAVE IN V_5 IN NORMAL ADULT SUBJECTS

	MEAN	±ST. DEV.	MIN.	MAX.
S in V_1 + R in V_5	19.9	5.6	(6	35)

The Q Wave.—No theoretical discussion of the production of waves will be attempted except to state that normally Q waves in the precordial leads were found only in QRS complexes reflecting left ventricular potentials.

Q waves were never seen in Lead V_1 or V_2, and rarely in Lead V_3, although a QS complex may occasionally be seen normally in Leads V_1 and V_2 (Fig. 1). Q waves were commonly seen in Leads V_4 to V_6, but were small, usually 1.0 to 2.0 mm. or less, and less than 0.04 second in duration. Q waves were occasionally seen in Lead V_3 when the transitional zone was displaced to the right and prominent R waves were present in V_3. In children and young adults, the Q waves in the left ventricular leads occasionally were as deep as 3.0 to 4.0 mm., but when this figure was obtained, the R wave was correspondingly taller. The maximum percentages of the Q/R ratio are summarized in Table VI, since by means of this ratio the Q waves may be quantitated more satisfactorily. When the amplitude of the QRS complex was 6.0 mm. or more, the Q/R ratio was less than 25 per cent. However, when the total QRS deflection was small, that is, 4.0 to 6.0 mm., then the Q/R ratio was occasionally greater than 25 per cent in our normal subjects (see aV_L in Fig. 2*A*). Q waves occurring with small QRS complexes, therefore, should be interpreted with caution.

TABLE VI. THE RATIO OF THE Q WAVE TO THE R WAVE (Q/R RATIO) IN NORMAL SUBJECTS

LEAD	MEAN	± ST. DEV.	MIN.	MAX.
V_1	0	0	(0	)
V_2	0	0	(0	)
V_3	0.025	0.002	(0	0.03)
V_4	0.04	0.032	(0	0.1)
V_5	0.07	0.039	(0	0.16)
V_6	0.087	0.043	(0	0.21)
aV_L	0.238	0.165	(0	0.75)
aV_R	4.97	2.96	(0	14.0)
aV_F	0.1	0.06	(0	0.28)

Q waves were also seen in normal subjects in the unipolar extremity leads. The deepest and most consistent were seen in Lead aV_R. In this lead the QRS complex was found to be negative throughout most of the duration of depolarization, usually being characterized by a QS complex. Frequently, however, a small R or R′ wave was seen either before or after the negative deflection (Figs. 2*A*, 4*B*, and 5). In the latter instance, the downward deflection of the QRS complex was a deep Q wave. The R wave rarely exceeded 3.0 mm. in aV_R; the maximum height of the R wave in aV_R was 5.0 millimeters.

The Q wave in Lead aV_F was similar to that found in V_5 or V_6, and reflected the transmission of the left ventricular potential to the left leg in vertical hearts. It usually was small, less than 25 per cent of the R wave. When the QRS complex is of small amplitude, the Q wave in Lead aV_F (just as is true in aV_L) may occupy a greater per cent of the R wave. These data are important as a base line for comparison with the findings in posterior myocardial

infarction. Occasionally, a QS complex was found in Lead aV_F in normal subjects with horizontal hearts, in association with a QS complex in Lead V_1. The RS-T segment and T wave were normal when a QS complex was present.

The Q wave in Lead aV_L was more difficult to evaluate, particularly when the Q and R waves were equal in size. Experience has indicated the importance of Q waves in Lead aV_L in the diagnosis of myocardial infarction, and Rosenbaum and his associates[21] have described their value in the diagnosis of

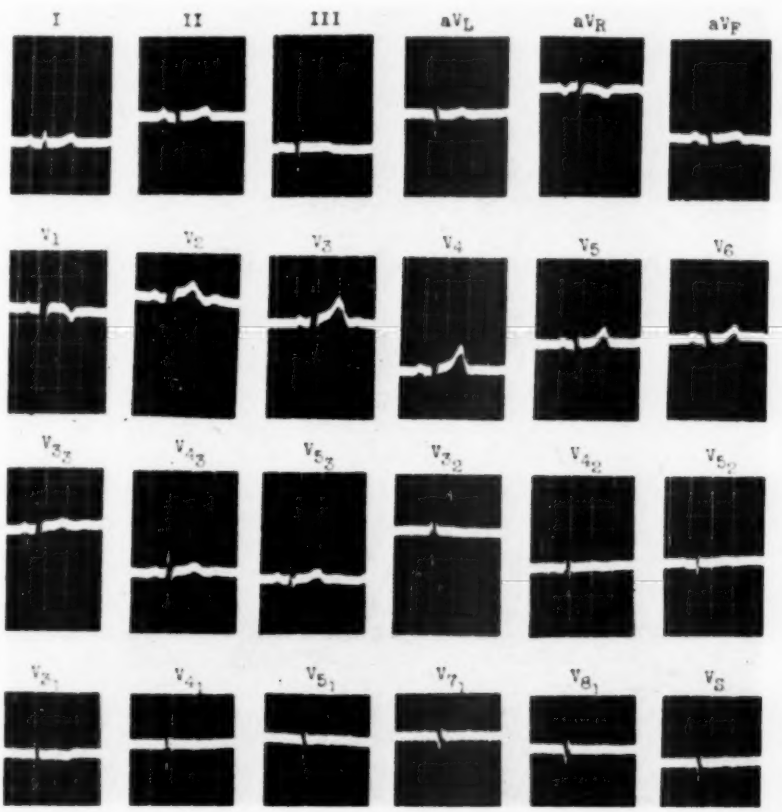

Fig. 3.—S. M., girl, age 9, U152854. Note the deep narrow Q wave with small R in aV_L, V_5 to V_8 in the first intercostal space (labelled V_{5_1} to V_{8_1}), the left shoulder (V_8), and at V_5 in the second intercostal space (indicated in fig. by V_{5_2}). Note that a small initial R is present in the fourth position in both the first and second intercostal spaces (indicated in fig. by V_{4_1}, V_{4_2}).

high lateral lesions. Therefore, it was considered extremely important to define the normal range of this wave. Usually the Q wave in Lead aV_L was small, both absolutely and in proportion to the R wave (Tables I and VI). On infrequent occasions, however, the amplitude of the Q wave equalled or exceeded that of the R wave in aV_L. In some cases it was difficult to determine whether or not a minute R wave preceded the negative deflection in Lead aV_L (Fig. 1,*E*). This was particularly true in vertical and semivertical hearts

with total voltage of the QRS complex in Lead aV_L less than 5.0 or 6.0 mm. (Figs. 3 and 4*A*); QS waves in Lead aV_L were also seen occasionally in subjects with vertical hearts, although commonly the pattern consisted of a small R and deeper S wave (Figs. 2*B* and 4*B*). Rarely, a deep, narrow Q wave with a minute R wave may be found in aV_L (Fig. 3). In these cases leads over the left lateral chest below the clavicle may show variably a small R and R′ and a deep Q with a minute R wave (Fig. 3). Review of those cases with a QS complex in aV_L revealed that all were associated with vertical or semivertical hearts, and with a normal RS-T segment and T wave.

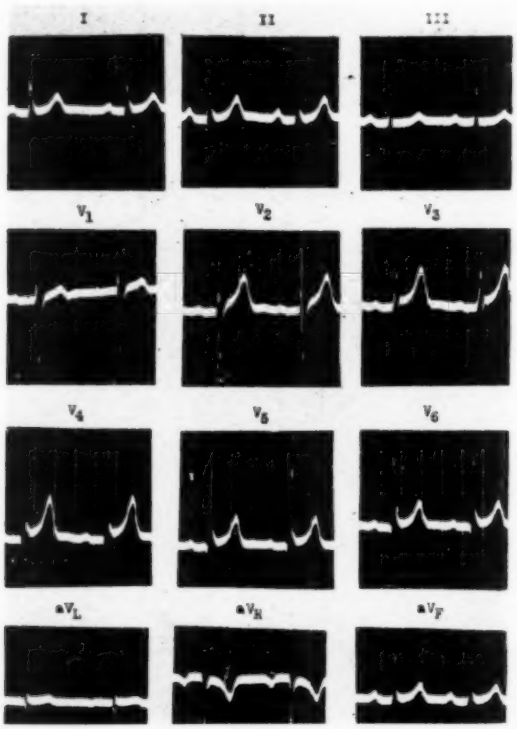

Fig. 4 *A*.—M. F., man, age 34. Semivertical heart with small initial and late R waves in aV_L. Note the elevated RS-T segments with their contour concave upward in the precordial leads.

In many of the normal subjects with prominent Q waves in the left arm lead, but with normal or absent Q waves in the left precordial leads (Figs. 1,*E* and 2*A*) exploratory leads were taken over the anterior precordium, in the second and third intercostal spaces, at Positions 4 to 7. This was done because of the occasional instance in which a high lateral myocardial infarction is manifested solely by a significant Q wave in the left arm lead.[21] It was found that the only normal subjects with significant Q waves in Lead aV_L with normal or absent Q waves in the left precordial leads were those in whom a vertical

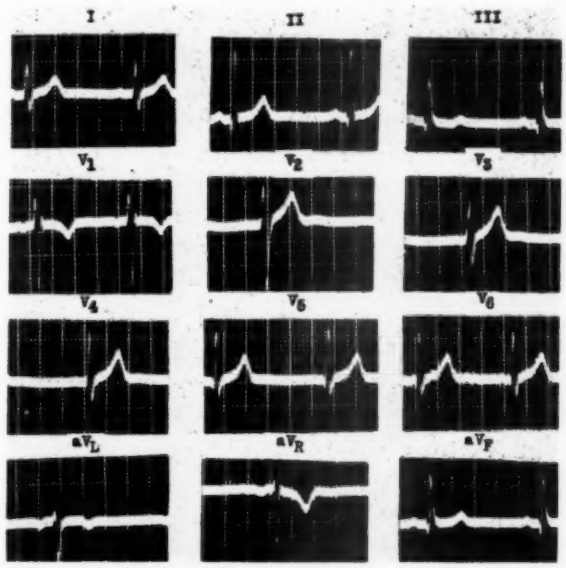

Fig. 4 *B*.—S. M., man, age 23. Obese; 152 pounds, 5 feet 4 inches. Vertical heart. Note the R′ and the inversion of the T wave of 2.5 mm. in V_1.

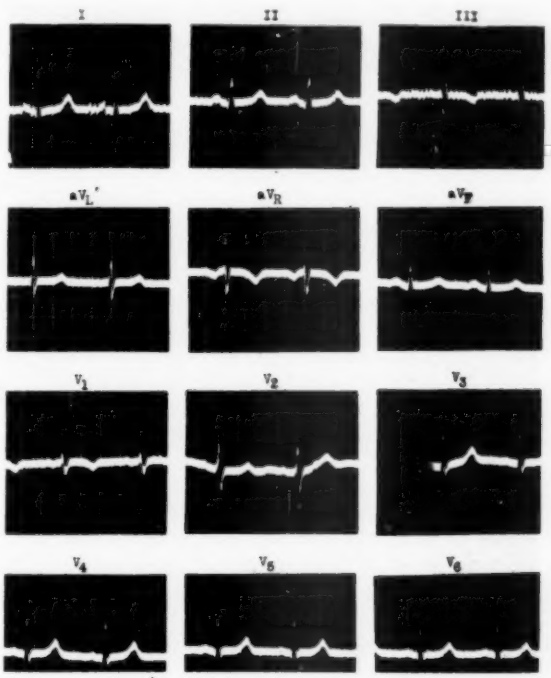

Fig. 4 *C*.—R. A., woman, age 58, U111922. Obese; 167 pounds, 5 feet. Intermediate heart. Note the deep Q in Lead III (5.0 mm., 55 per cent of tallest R wave in standard leads). Minute Q in aV_L. The Q wave in Lead III is the result of the relative negativity of the left leg as compared to the left arm.

or intermediate position was present. Exploratory leads high over the anterior precordium did not reveal the findings characteristic of anterior myocardial infarction. In these patients, just above or just below the clavicle, or at the point of the shoulder, QRS complexes were obtained which resembled those of the left arm lead (Fig. 3). These complexes were interpreted as being the proximal extension of the positional variations noted in Lead aV_L. A study of the right arm lead in these cases revealed prominent Q waves and/or minute R or R′ waves; these findings are consistent with a posterior rotation of the apex of the heart, so that both the right and left arm leads face the cavities of the ventricles.[7]

Intrinsic Deflection and Ventricular Activation Time.—The maximum ventricular activation time in our normal subjects was 0.035 second in Lead V_1 and 0.055 second in Leads V_5 and V_6. In no normal subject was the ventricular activation time as much as 0.04 second in Lead V_1 or 0.06 second in Lead V_5 or V_6. The time of onset of the intrinsic deflection was consistently greater in the left precordial leads than in the right precordial leads. This is clearly shown in Fig. 1, which demonstrates that the peak of the R wave occurs earlier in the QRS interval in leads from the right precordium than in leads from the left precordium. A separate study[22] utilizing six simultaneous precordial leads confirmed the normal range and maximum date on ventricular activation time in normal subjects.

The RS-T Segment.—Elevation of the RS-T segment (up to 3.0 mm.) was not uncommon in Lead V_1, V_2, or V_3, but rarely exceeded 1.0 mm. in Leads V_4 to V_6 (Fig. 4*A*). The contour in these instances was concave upward, with a rapid ascent, and in no case was the RS-T segment horizontal or convex upward so as to simulate the pattern seen in coronary disease. Depression of the RS-T segment was more rarely seen and was never greater than 0.5 millimeter. When the RS-T segment was depressed, the contour was similar to that seen when the segment was elevated, that is, concave upward. Apparently a depressed RS-T segment of minor degree is of greater significance than a similar change in the RS-T segment that is elevated.

T Waves.—Data on the T waves are summarized in Table I. The ratio of the R wave to the T wave in the corresponding lead was also obtained so as to have more quantitative information in regard to T waves (Table VII). Inversion of the T wave was common in Lead V_1 in normal subjects, infrequent in V_2, rare in V_3, and was never found in V_4 except in children. The maximum inversion of the T wave in V_1 was 2.5 mm. in adults. Furthermore, in the children studied (our findings in children agree essentially with those reported by Battro and Mendy[11]) all had normal T waves in Leads V_5 and V_6, with prominent R waves. In the cases in which inversion of the T wave was present in V_2, V_3, or V_4, the leads to the right also had inverted T waves. An inverted T wave in any precordial lead with a normally upright T wave in the next position to the right was not found. The inverted T waves in Leads V_1 and V_2 were as a rule relatively small, the maximum being 2.5 mm. in adults (Figs. 2*B*, 4*B*, and 4*C*). The inverted T waves usually were associated with

a slightly convex and slightly depressed RS-T segment (Fig. 1). The R waves were small in the leads in which the T wave was normally inverted, the S wave was prominent, and no Q waves were visible; such complexes were clearly of right ventricular origin. Inverted T waves were not seen in the normal subjects when the QRS complex reflected left ventricular potentials. When the transitional zone was displaced to the left, the T wave occasionally was inverted in Leads V_2 and V_3; inspection of the R/S ratio clearly indicated the right ventricular origin of the complexes.

TABLE VII. THE RATIO OF THE R WAVE TO THE T WAVE (R/T RATIO) IN NORMAL SUBJECTS

LEAD	NO.	MEAN	ST. DEV.	MIN.	MAX.
V_1	59	1.4	0.9	(0.3	7)
V_2	145	1.4	1.4	(0.2	12)
V_3	150	1.9	1.6	(0.3	13)
V_4	150	3.1	2.3	(0.3	9)
V_5	150	3.5	1.6	(1.0	9)
V_6	150	4.1	1.9	(1.7	10)
aV_L	91	2.6	1.9	(0.1	10)
aV_F	142	4.6	3.2	(0.3	14)
aV_R		0	0	(0	)

The maximum upright T wave in Lead V_1 was 4.0 millimeters. The tall T waves in Leads V_2 and V_3 that occasionally occur normally in these leads (Table I) must be kept in mind when tall T waves in the right precordial leads are being considered to support a diagnosis of posterior myocardial infarction. The T wave was frequently found to be inverted in the left arm lead in vertical hearts (Figs. 2*B* and 5). Table I defines the range of this wave in nineteen cases of right axis deviation with vertical hearts. It was found that the maximum inversion of the T wave in Lead aV_L, even in a normal vertical heart, was 2.5 mm. (Fig. 5). In no instance in which the R wave in Lead aV_L was 5.0 mm. or taller was the T wave inverted. All inverted T waves in aV_L seen in the normal vertical hearts occurred with small R waves and prominent S waves, or with QS complexes. When the height of the R wave was 3.0 to 4.0 mm., the T wave rarely was inverted more than 0.5 mm., and often was flat (Fig. 6). This was also true of the left leg lead. In no normal subject was the T wave in the left leg lead inverted when the R wave exceeded 5.0 mm. in height. Since the R wave in Lead aV_L was upright in subjects with horizontal hearts with left axis deviation, it should be noted that the T wave in aV_L was not inverted in any of the subjects with normal horizontal hearts (Figs. 1 and 7).

Transitional Zone.—As the precordial electrode was moved across the precordium from the right to the left, an intermediary zone was noted which varied from precordial Positions 2 to 6. Usually this transitional zone was demonstrated in Lead V_3 or V_4. The transition was occasionally abrupt, so that ventricular complexes one position apart varied strikingly (Figs. 4*A* and 8), or was extended over several positions. To the right of the transitional zone, the ventricular complexes were clearly of right ventricular origin, with a small

R, prominent S, and absent Q wave. To the left of the transitional zone, the ventricular complexes were clearly of left ventricular origin and manifested a prominent R, small to absent S, and perhaps a small Q wave. When the transitional zone was displaced far to the left, Lead V_5 or V_6 showed complexes of right ventricular origin. In these cases, leads farther to the left, such as V_7 and V_8, demonstrated the typical left ventricular potentials. This is of importance when right ventricular hypertrophy is being considered, because

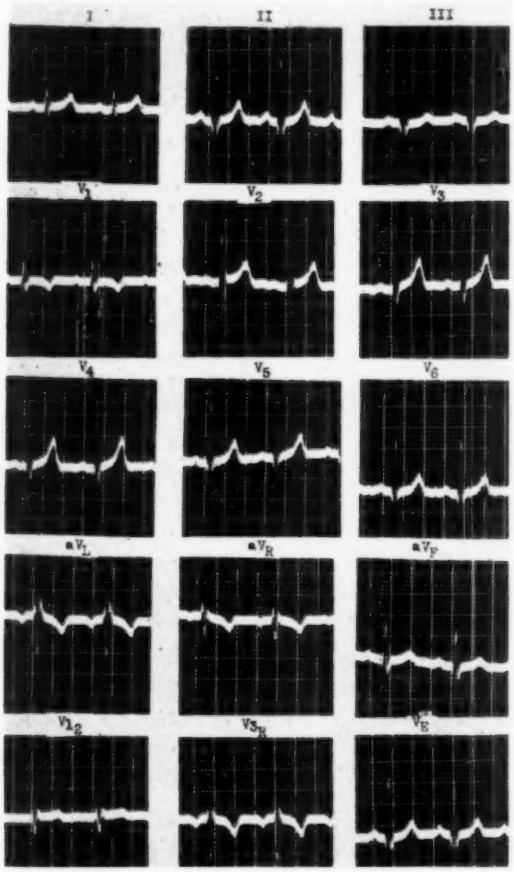

Fig. 5.—F. H., woman, age 35. Vertical heart with counterclockwise rotation of the heart and transitional zone between Positions 2 and 1. Leads over the right precordium (V_{3R} and V_1 in the second intercostal space marked V_{12}) are of right ventricular origin, while V_E (xiphoid) resembles V_6.

characteristically in this condition a small R and prominent S wave occur in the left precordial leads. More rarely, when the transitional zone is displaced to the right, leads from precordial Position 2 may demonstrate left ventricular potentials and may also simulate right ventricular hypertrophy, in which prominent R waves occur over the right precordium. When the transitional zone was displaced to the right in our normal subjects, leads farther to the right

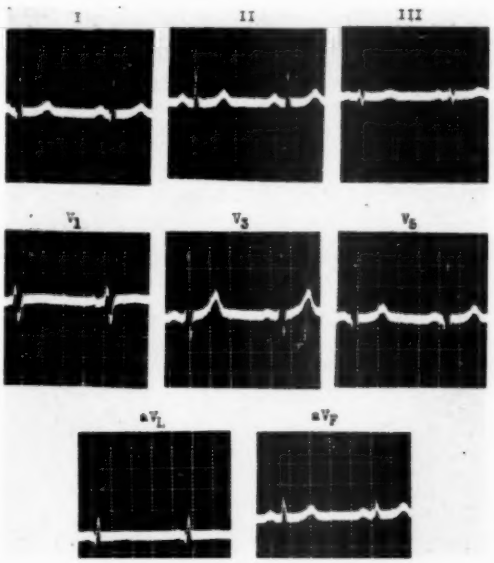

Fig. 6.—W. T., man, age 52. Normal heart confirmed by autopsy. Q wave 25 per cent of the R wave (1:4) in aV_L with flat T wave. Interpretation of Q and T waves in Lead aV_L should be cautious when the total voltage of the QRS complex is small.

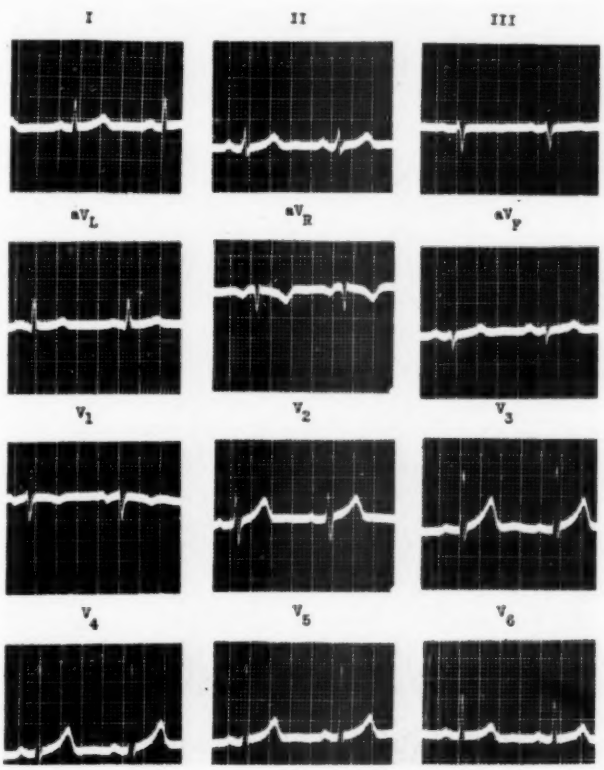

Fig. 7.—H. H., man, age 57, U78776. Horizontal heart, axis −20 degrees.

demonstrated the typical right ventricular potentials (Fig. 5). The form of the QRS complex in the transitional zone was occasionally bizarre, with variable R and S waves, often with slurred and notched QRS complexes. This type of transitional zone QRS complex was only rarely seen in more than one position.

Rotation of the Heart.—At times, in records obtained from normal subjects, unusual axis deviation, ususual position of the transitional zone, or the appearance of Q waves in the left arm lead suggested the possibility of unusual rotation of the heart. Posterior displacement of the apex has been already referred to in the discussion of the Q waves. Very infrequently, marked clockwise rotation of the heart on its longitudinal axis (viewed from the apex) was assumed in subjects in whom the transitional zone was displaced to the left. In these cases, the transitional zone was demonstrated in Lead V_6; left ventricular potentials were obtained over the right posterior thorax, from the right upper abdomen, and from the right lateral chest. Right ventricular potentials were obtained over precordial Positions 1 to 5, the ensiform process of the sternum, and high over the right anterior chest (Fig. 8). This transmission of potentials suggests that clockwise rotation of the heart was present, so that the potential changes of the left ventricle were noted over the left and right posterior chest and were transmitted anteriorly to the right upper abdomen and right lateral chest. Study of the unipolar extremity leads in relationship to the usual six precordial leads and exploratory leads over the precordium to the left and right were often helpful in demonstrating unusual rotation of the heart. The possibility of cardiac abnormality was always considered when bizarre rotation of the heart was encountered.

Unipolar Extremity Leads.—The pattern of the unipolar extremity Leads aV_L and aV_F depended upon the electrocardiographic position of the heart, and therefore upon the electrical axis of the heart. If the heart was horizontal and the axis shifted to the left, the normal pattern in Lead aV_L was similar to that seen in the left precordial leads (to the left of the transitional zone), and consisted of a prominent R wave, a small to absent S wave, an upright P wave, an upright T wave, and possibly a small Q wave. When the heart was vertical and the axis was shifted to the right, the normal pattern Lead aV_L was similar to that obtained from the normal right precordial Leads V_1 and V_2, and consisted of a small R wave, a prominent S wave, and variable P and T waves. The basic pattern in Lead aV_F in vertical hearts when the axis was shifted to the right resembled the left precordial Leads V_5 and V_6, since the left ventricle faced the left leg. When the heart was horizontal and the axis was shifted to the left, the normal pattern in Lead aV_F resembled the right precordial Leads V_1 and V_2. When the heart was intermediate in position, and the potential changes of the left ventricle were transmitted to both the left arm and the left leg, both aV_F and aV_L resembled the left precordial Leads V_5 and V_6, but neither had very great voltage. When the QRS complex was upright in both aV_L and aV_F, that lead which most nearly resembled the left ventricular leads more clearly reflected the position of the heart (Fig. 6;

Q wave in aV_L and V_5). The right arm lead, as can be seen from the figures, almost invariably was negative through most of the QRS interval. This is probably due to the fact that the right arm usually faces the cavities of the heart, which are essentially electronegative, since the spread of activation is toward the epicardium, from the endocardium. The QRS complex in Lead aV_R was variable and consisted of either a QS complex, a small R, deep S, and small R′, or a deep Q and small R wave. The R or R′ in Lead aV_R rarely exceeded 3.0 mm. and in none of our normal subjects exceeded 5.0 millimeters.

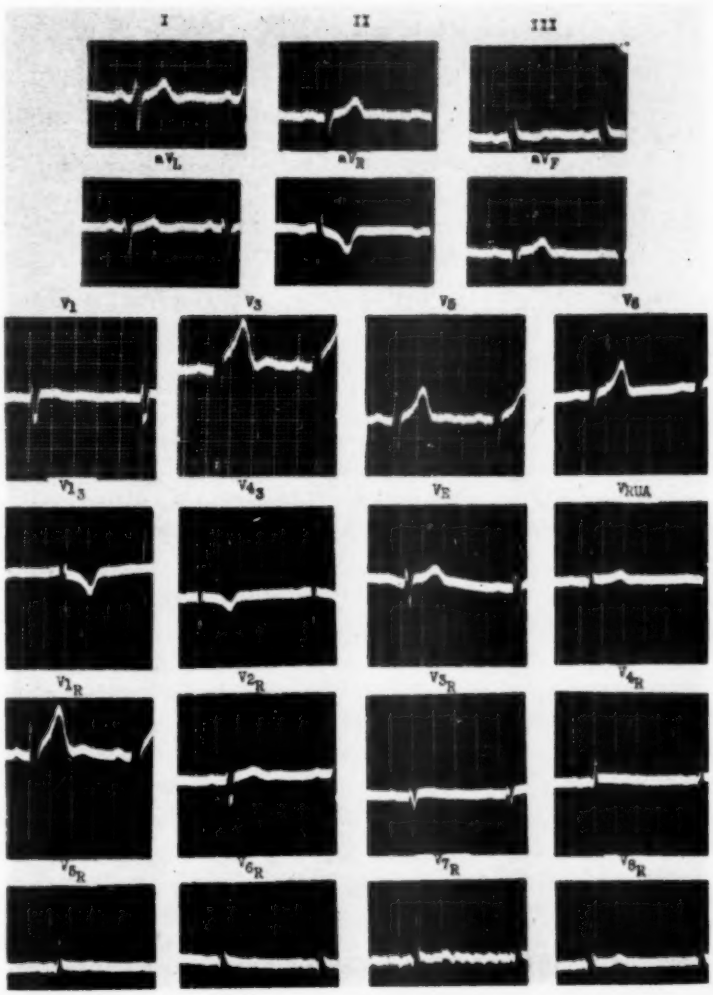

Fig. 8.—W. D. L., man, age 20, U150427. March 18, 1948. Left hydrothorax in 1938. Fibrocalcification left upper pulmonary lobe. No cardiac enlargement. Unusual pulsation in left superior cardiac border. Transitional zone between Positions 5 and 6. Left ventricular complexes in V_6, V_{4R} to V_{8R} (right side), and V_{RUA} (right upper abdomen). Right ventricular complexes in V_1 to V_5, V_{1R} to V_{3R}, and V_E. Marked clockwise rotation of heart.

The right arm lead, aV_R, may show a small initial R wave and still reflect the potential changes of the right ventricular cavity, since intracavity leads may reveal a small initial R wave from the right ventricular cavity[23,24,25] The P wave in Lead aV_R was usually inverted, the RS-T segment isoelectric or slightly depressed, and the T wave always inverted. In none of the normal subjects was an upright T wave found in aV_R.

DISCUSSION

The importance of clearly defining the normal range of the values in the unipolar leads is self-evident, especially when borderline findings require interpretation. The frequency or rarity of a given finding in normal subjects will permit a statement as to the probability of the normality of the finding in question. Furthermore, a knowledge of the approximate percentage in which several given findings may be expected in normal subjects will allow interpretation to be more accurate, since infrequent abnormalities, when multiplied, are geometric and not additive in significance. Thus, in a young patient with hypertension, the presence of the following findings individually would be borderline:

1. A horizontal heart with marked left axis deviation, *or*
2. A relatively low to flat T wave in Leads I, V_5, or aV_L in the presence of tall R waves in these leads, *or*
3. A ventricular activation time of 0.55 second in V_6, *or*
4. A heart with the voltage of R in $V_5 + S$ in $V_1 = 35$ millimeters.

But if several or all of the findings were present together, the chances that these several abnormalities (each to be expected infrequently in normal subjects) were without significance would be remote indeed.

The importance of the unipolar precordial and extremity leads in permitting a more rational interpretation of the electrocardiogram became obvious during the study. Variations in the standard limb leads which previously had been interpreted on an empirical basis were explained more rationally by a consideration of such factors as the electrocardiographic position of the heart, the position of the transitional zone, and the rotation of the apex of the heart either anteriorly or posteriorly on a transverse axis, or in a clockwise manner on a longitudinal axis, et cetera. Proper interpretation of unusual rotation of the normal heart is most important, because records obtained in such cases simulate ventricular hypertrophy or myocardial infarction and the differentiation is obviously of great significance. The standard limb leads are indirect leads and the data obtained from them are not comparable to the data obtained by direct leads from the epicardium in animals or by precordial leads in human subjects. The standard limb leads are bipolar leads and record the composite differences in potential of two unipolar extremity leads and not that of a single extremity. The two unipolar extremity leads used in recording a standard limb lead may each have potential changes which may be additive or may neutralize each other, so that the standard limb lead may not permit the actual condition to be visualized. The standard leads, furthermore, reflect the contri-

bution of all portions of the heart, and the effects of small lesions may be overshadowed by the effect of the great mass of normal myocardium. Multiple precordial leads permit visualization of both right and left ventricular changes, whereas a single precordial lead, if it constitutes the sole evidence presented, has the disadvantage of reflecting potential variations largely of that portion of the heart which lies under the electrode.[1] With variations in the position of the transitional zone and unusual rotation of the heart, a fixed position for a single precordial lead would obviously create many difficulties in interpretation. Furthermore, accurately relocating the exact precordial position when serial records are required, as in myocardial infarction, is most difficult, and multiple leads most easily allow serial changes to be interpreted.

The significance of a small R′ deflection in V_1, which was noted in about 5 per cent of the normal subjects (Fig. 4*B*), is not clear. Exploratory leads over the right precordium failed to give additional information unless they revealed more definite evidence of delayed conduction through the right ventricle. The conus of the right ventricle is the last part of the right ventricle to be activated,[18] and it is possible that this late R′ deflection represents activation of this area or of the posterior surface of the left ventricle.[24] The R′ in our cases usually was small, less than 0.04 second in duration, and the initial small R and prominent S deflections were similar to the typical ventricular complex obtained over the normal right ventricle. Serial records in these cases occasionally revealed a small, late R′ deflection on one occasion and a notched S without an R′ deflection in another. When the R′ was taller than the initial R wave and was 0.04 second or more in duration, when the S wave was small and the total QRS complex was 0.10 second or more, the possibility of an incomplete or complete right bundle branch block was considered.

The rarity of a horizontal position of the heart in individuals under the age of 40 years was a surprising finding. This was particularly true in many robust, slightly obese, and sthenic individuals. Only two of our subjects under the age of 39 years had a semihorizontal or horizontal heart. The finding, therefore, of a horizontal heart in a young individual should raise doubts of normality, particularly if an anatomic cause of such a cardiac position is not obvious.

The data on voltage and on the various ratios presented were of value in a companion study on right and left ventricular hypertrophy.[9-19] Abnormal voltage of the QRS complex often was the initial finding in left ventricular hypertrophy, and the data on voltage presented in the present series of 150 normal subjects have not required change in a review of 1,500 subsequent normal unipolar records taken in the Electrocardiographic Department of the University of California Hospital.

Quantitative data presented on the height of the normal T wave may prove helpful in determining the normality of the troublesome low T wave. Since depolarization has a definite relationship to the succeeding repolarization, the height of the T wave was related to the height of the R wave in the same lead. Our data indicate that a T wave less than 10 per cent of the height of the R wave in the left precordial leads is to be viewed with suspicion (Table VII).

The wide range of the normal variations of the Q wave in the left arm Lead aV_L requires conservatism in the interpretation of the significance of such a finding. The sole use of a percentage figure in relation to the R wave is unreliable because of the occasional high Q/R ratios in normal subjects with small QRS complexes in Lead aV_L, and because of unusual rotation of the heart so as to direct the potentials of the ventricular cavities toward the left arm. The interpretation is at times made more difficult because in different complexes in the same lead, or in different leads on the same or on succeeding records, the QRS complex in Lead aV_L may at one time consist of a QR pattern, and at other times of an rSr′ or rS type of complex. This variability may be seen also in high left precordial exploratory leads, when in successive positions the QRS complex may consist of an rSr′ or of a QR pattern (Fig. 3). Inspection of these records suggests that these normal Q waves are sharp and of short duration, and not associated with characteristic RST-T changes of coronary insufficiency. Whether the QR complex in Lead aV_L is due to posterior rotation of the heart on a transverse axis, as suggested by Goldberger,[7] cannot be proved from our data.

SUMMARY AND CONCLUSIONS

1. A statistical study of the unipolar precordial and extremity leads of 150 normal subjects is presented.

2. The mean, standard deviation, and the range of the amplitude of the Q, R, S, and T waves and of the ventricular activation time (time of onset of the intrinsic deflection) have been determined in these normal subjects and tabulated.

3. To present certain of the data in further detail, the following ratios and sums have been determined and their significance discussed: (a) the Q/R ratio; (b) the R/T ratio; (c) the R/S ratio; (d) the R/S ratio in V_5 divided by the R/S ratio in V_1; (e) the sum of the amplitudes of the R wave in V_1 and the S wave in V_5; (f) the sum of the amplitudes of the S wave in V_1 and the R wave in V_5.

4. The electrocardiographic position of the heart in these normal subjects is discussed, and the infrequence of a horizontal heart in persons under the age of 39 years (in the absence of gross obesity or late pregnancy) is pointed out.

5. The variability of the Q wave in the left arm lead is described, and the significance of total QRS amplitude, rotation of the heart, and other factors important to proper interpretation are discussed.

We are grateful to Miss Julia Haug, Miss Nancy Gelardi, Mrs. Doris Tuttle, and Mrs. Angelina Galante for technical assistance, and to Dr. John C. Talbot for advice in regard to the statistical methods.

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THE HEART MUSCLE AND THE ELECTROCARDIOGRAM IN CORONARY DISEASE

II. Difficulties of Description and Illustration of Ventricular Muscle Lesions, With a Method for Their Graphic Representation in a Myocardial Map

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With the progress which has been made in clinical and electrocardiographic diagnosis of myocardial damage, the precise localization of lesions at autopsy has become essential. In the first paper of this series the principles of a pathologic technique adequate for clinicopathologic correlation studies have been considered.[1] This second paper is concerned with the organization of the pathologic data once they have been collected. Systematic gross and microscopic scrutiny of the myocardium is only the first step in the study of infarcts and scars. The information gained connot be put to use until it has been adequately recorded in some permanent form. This is not easy. The heart muscle and its lesions are difficult to describe in words or to illustrate in pictures. Indeed, all writing about the myocardium has suffered from the inadequacy of descriptive and illustrative methods.

The present study discusses the difficulties of describing myocardial damage verbally, the necessity for resort to pictorial methods of recording, and the reasons why such methods of illustration have been unsatisfactory. A solution to the problem is offered on the basis of a geometric survey of the damaged areas seen in serial slices, which permits graphic representation of lesions and their important anatomic relationships. A convenient schema or myocardial map of the left ventricular and septal muscle and the major coronary branches will then be described for use in the presentation of data in subsequent sections of the report.

THE DEFECTS OF VERBAL RECORDS

The standard terminology for cardiac ventricular areas is in itself a major difficulty. The usual divisions are right and left ventricles, apical and basal regions, and various surface areas: anterior, lateral, posterior, and perhaps diaphragmatic, for each chamber. Endocardial areas have been named from

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the overlying surface, except for the part without any epicardial surface, the septum. While these terms sound simple and definite, they are seldom defined, and are used as if they referred to clear-cut subdivisions of the heart, with the same meaning for clinician and pathologist.

It is usually forgotten that the heart is so lacking in convenient landmarks that even under the most favorable circumstances, for example when the pathologist has the organ in his hands, it is difficult to establish the limits of surface areas except along the interventricular grooves. The anterior, lateral, and posterior regions fade gradually into each other so that their limits are mainly arbitrary. As a rule, the middle of the lateral wall of the left ventricle is taken to lie halfway between the anterior and posterior grooves, the anterolateral and posterolateral regions being somewhere intermediate. The conventional subdivisions of the left ventricular circumference are thus not very precise. They are especially unsatisfactory near the apex or near the endocardial surface, where distances are much shorter. The right ventricular surface is subdivided at the acute margin, which, as a rule, is clearly marked at autopsy.

Intermediate distances between apex and base cannot be measured conveniently at all, since the heart has no transverse landmarks below the atrioventricular grooves. Attempts to escape the difficulty by linear measurements are unavailing because the significance of any distance in centimeters will vary with the size of the heart and the position at which the measurement is made. It has generally been found best to make rough subdivisions of the distances between such landmarks as there are, making reference to such areas as "the apical third of the posterolateral wall," "the anterior basal portion of the septum," and so forth. Clearly, however, the pathologist consciously or unconsciously is relating everything (in a not very quantitative way) to the atrioventricular and interventricular grooves and the left ventricular apex.

To the clinician, on the other hand, the position of the interventricular grooves and, hence, of the adjacent myocardium cannot be accurately known. Study of the cardiac silhouette or of the precordial patterns of the electrocardiogram provides data about pulsation, contour, and electrical activity which may vary greatly in anatomic significance with the position of the heart in the chest. Furthermore, with the rare exception of conveniently placed calcification, there is no way of estimating with certainty the relation of the postmortem position of the heart in the chest to that during life.

Despite these difficulties, the same terms are used by both clinician and pathologist. Identical words may thus have considerably different meanings. "Anterior" to the pathologist means proximity to the anterior interventricular groove, regardless of the heart's position in the chest. To the clinician, "anterior" may mean the parts of the heart presented to the precordium or even the myocardium affected by anterior descending coronary artery occlusion. "Posterior" has an analogous variety of meanings and in addition is often not clearly distinguished from "diaphragmatic" and "posterolateral" so far as the left ventricle is concerned. "Lateral," for the clinician, means the part of the left ventricle he sees pulsating fluoroscopically which is directed toward the left axilla and shoulder and separated from the chest wall by lung. The

muscle actually comprising this region will, of course, vary, in the pathologist's terms, from "anterolateral" to "posterolateral," depending on cardiac rotation. "Subendocardial" is vaguely used by both the clinician and the pathologist. In general, it means the myocardium that lies nearest the ventricular cavities, designating a lack of surface involvement, but it is seldom stated whether the term referes to the trabeculae carneae, the underlying wall proper, or both.

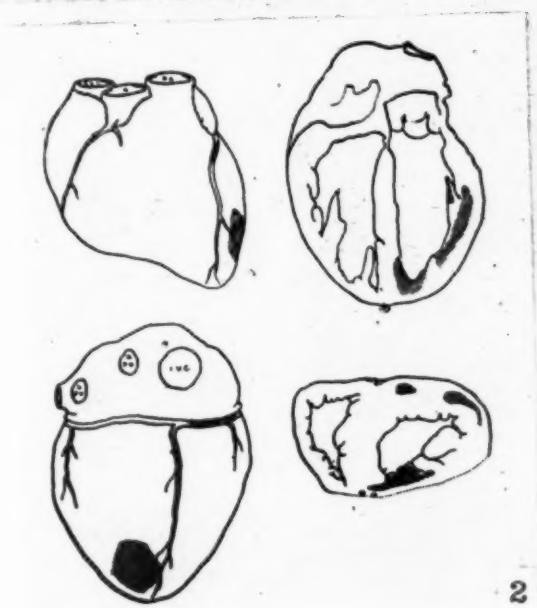
As a result of the loose employment of a nomenclature that was never very exact, it is only possible to specify myocardial areas precisely by tacking on qualifying and explicatory terms. Autopsy reports thus become more wordy and involved as their accuracy increases; yet protocols which sound simple and clear are very likely to be inadequate.

While the gross anatomic form of the ventricular muscle mass, in the substance of which lesions lie, is difficult to describe as a whole or to divide into smaller regions, this is only part of the descriptive difficulty. Infarcts and scars conform in shape not to the conventional subdivision of the ventricles but to the areas of distribution of the epicardial coronary arteries. Yet these areas show enough anatomic variation from anomaly or collateral circulation to be unsuitable as a basis for indicating the shape of lesions. Moreover, the infarcts and scars themselves, far from resembling the simple circular, oval, or wedge-shaped areas conventionally described in medical literature, appear as curved, plate-like areas of fibrosis or necrosis which have irregular borders and may vary in thickness in different parts of the ventricular wall. Although generally discrete and clear-cut in their form, these lesions are so poorly adapted to verbal description that no reforms in nomenclature seem to offer hope in solution of the difficulty.

On the other hand, forms difficult to describe are often easy to draw. A number of investigators, noting this, have supplemented their protocols by pictures. Though the heart also resists illustration stubbornly, there seems little question but that this is a more fruitful approach. Prior to 1935 not many investigators were interested in myocardial illustration, but since that time there have been more systematic attempts to supplement protocols by photographs, drawings, or both. It is worth while to examine some of these methods.

METHODS OF ILLUSTRATION

Of the few investigators who have used photographs for the routine recording of lesions, one group deserving special mention is Büchner, Weber, and Haager (1935),[2] whose monograph illustrated myocardial damage by combining photography with an unusual method of opening the heart. A longitudinal slice was made down the lateral wall of the left ventricle and carried through the center of the septum to the anterior right ventricular wall, almost cutting the heart into anterior and posterior halves. The limits of any lesion that photographed poorly were indicated by a line drawn on the photographic print (Fig. 1). This had to be done frequently, since the greater part of most lesions was buried in opaque muscle.



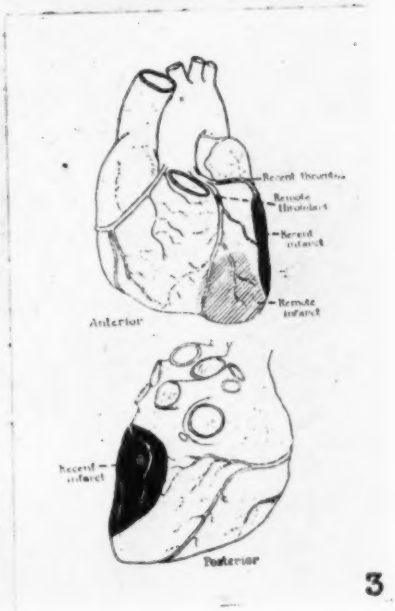


Fig. 1.—A heart cut into anterior (left side of photograph) and posterior halves. An old, large "anterior" lesion involves the apex and septum. (*a*), A recent "posterior" lesion that does not show well in the photograph has been indicated by the heavy line (solid in the left ventricle, broken in the right). (From Büchner and associates, 1935.[2])

Fig. 2.—Areas of scarring in diagrams of the external surfaces (left), a single longitudinal slice (upper right), and a single transverse slice (lower right). (From Burton and associates, 1930.[3])

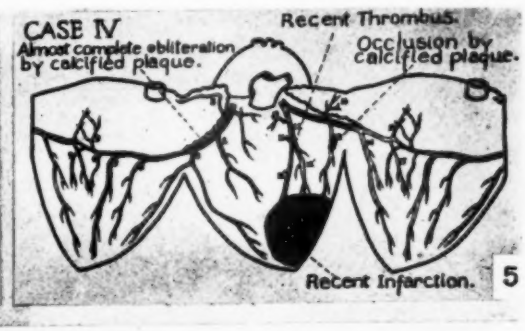
Fig. 3.—An old "anterior" and a recent "lateral" lesion, with the related coronary lesions, are indicated on conventional anatomical drawings of the exterior of the heart. (From Thomson and Feil, 1944.[4])

Photography has not proved a good method for recording routinely the appearance of infarcts and scars. An occasional lesion may be displayed well, but many scars show up poorly in photographs: the color changes in acute lesions, which are often subtle, fail to be recorded, while irregularity of fixation, obvious to the eye, may be deceptive in a picture. Furthermore, the consistency of tissue, almost as important as color in the gross evaluation of lesions, cannot be recorded by the camera. At best, photographs provide an incomplete report and almost always require supplementation or retouching.

Several types of drawings have been employed in the last two decades to illustrate myocardial lesions. Burton and associates (1930),[3] in their four case reports, drew the outline of scars on a diagram of the uncut heart, supplementing this by sketches of a single longitudinal and transverse slice of the ventricles (Fig. 2). Thomson and Feil (1944)[4] used a similar type of drawing of the cardiac surfaces (Fig. 3). Jervell (1935)[5] indicated the site of lesions in a sketch of the routinely opened left ventricle as seen on its endocardial aspect, the lateral wall flap being turned back and the septal wall exposed (Fig. 4). Saphir and associates (1935)[6] adopted the Spalteholz schema of the coronary circulation[7] (Fig. 6) to a sketch of the partly opened heart (Fig. 5). Schlesinger (1938),[8] in his studies of the coronary circulation, further modified the Spalteholz schema by actually dissecting the heart so that its main epicardial arteries could be laid in one plane for radiographic study. The method consists essentially of cutting out the septum. This converts the heart into a muscular bag which, after being opened longitudinally down the anterior interventricular groove, can be laid flat. The technique is, of course, designed primarily to produce a picture of the coronary arteries, but has been also used to indicate the position of areas of myocardial damage by outlining them on the roentgenogram[8] (Fig. 7) or on a drawing made therefrom.[9] This method has acquired considerable popularity.

There are serious disadvantages to all the illustrative methods mentioned so far. In the first place, none of them shows the heart in a manner well fitted for the display of its most common muscle lesions. Much space is given to the right ventricle, where large lesions are rare. This is accomplished at the expense of proper illustration of the septum, which has to be made a subsidiary part of the picture or shown as a separate fragment. Since the septum is often infarcted, the infrequent reporting of its lesions testifies to a frequent failure in exploration or illustration of this region. Furthermore, with the exception of Büchner's illustrations,[2] no investigators have provided in their drawings a record of the thickness of the heart wall affected by myocardial lesions. The types of illustration chosen have thus tended to affect unfavorably the data collected. It is unfortunate that certain types of myocardial lesions which are difficult to record have proved to be common and important.

Second, none of the illustrative methods shows lesions in such a way that they can be related to familiar cardiac landmarks. It happens that while the greater part of myocardial damage is found in the deeper layers,[10] the interventricular grooves which define the limits of the right, left, and septal ventricular musculature are on the outer surface of the heart. When the inside of



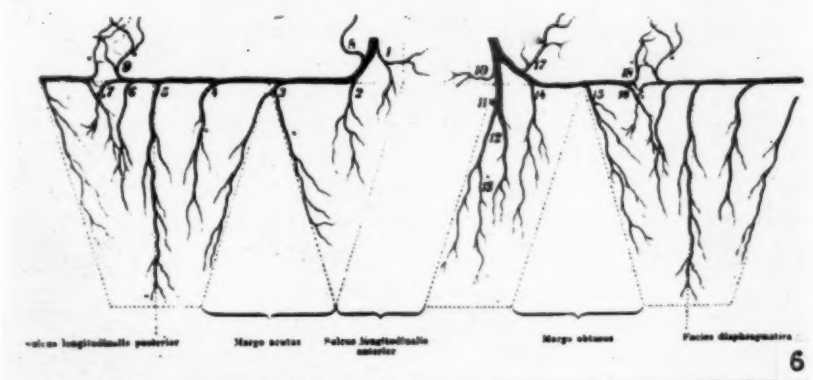


Fig. 4.—A large "anterior" lesion and small "lateral" and "posterior" lesions have been indicated on a drawing of the opened left ventricle. (From Jervell, 1935.[5])

Fig. 5.—A recent "anterior" lesion and related coronary lesions are indicated on a diagrammatic compromise between the routine Virchow method of opening the heart and the Spalteholz schema (see Fig. 6). (From Saphir and associates, 1935.[6])

Fig. 6.—A diagrammatic representation of the main surface coronary arteries as they appear when laid flat. No septal branches are shown. (From Spalteholz, 1924.[7])

Fig. 7.—A roentgenograph of a heart in which a large "posterolateral" lesion has been indicated by the dotted line. The heart has been opened by a special technique which enables the main arteries to be flattened out in one plane. The septum has been cut out and appears as a separate piece. (From Schlesinger, 1938.[8])

the heart is illustrated (Jervell[5] and Büchner and associates[2]), the lesions are shown best but the landmarks are not evident; when the outside is illustrated (Thomson and Feil[4] and Saphir and associates[6]), the landmarks are seen well but the lesions are not. In either circumstance the general reader tends to lose his bearings when looking at the illustration, which thus fails of a good deal of its purpose in making the relevant pathologic anatomy clear, especially where electrocardiographic correlation is a main objective.

The third disadvantage arises from the second. Because the relation of damaged myocardial areas to standard landmarks is not established, transfer of data from the anatomical specimen to any of the illustrations so far discussed can only be done in an approximate way, unless the heart has been opened exactly in the manner depicted by the particular illustration. An accurate sketch or a retouched photograph can then reproduce the appearance of the specimen, but the price is likely to be a less satisfactory autopsy. The best form of illustration for the heart is not ordinarily a picture of the fragments which result from a dissection thorough enough to obtain complete facts. Systematic exploration of the heart muscle thus has tended to be discouraged rather than stimulated by the employment of the usual illustrative techniques.

There is, nonetheless, a real need for depicting lesions in the heart muscle. The disadvantages of the usual methods—their poor adaptation to the common types and characteristics of muscle damage, their failure to relate lesions to standard landmarks, and their tendency to interfere with the thoroughness of an autopsy—call for improvement in, but not abandonment of myocardial illustration. Indeed, the very analysis of the disadvantages makes it possible to formulate the principles which must underlie any adequate pictorial description of this sort.

The first consideration must be a *pictorial record* which preserves the findings of a thorough autopsy in permanent, accurate, and complete form. Because of the deficiencies of verbal description, already discussed, the pictorial record must replace the cumbersome and less precise written protocol. Second, it will usually be necessary for the purposes of any particular investigation to select from the full pictorial record those facts which bear directly on the problem at hand and make another illustration more suited to easy analysis of data and comparison of hearts throughout a series of cases. This second type of illustration may be called a selective or *reconstructive schema*, its primary purpose being not to record data but to display them in a useful way. Both types of illustration are valuable, but it is clear that the second type is dependent on the first. The pictorial record must be adequate; otherwise no worthwhile selective schema can be based on it. Most illustrations of the heart fail both as accurate records and as convenient schemata because they attempt too much in a single picture. The solution of the problem is to keep the two steps—recording and reconstructing—quite separate, proceeding to the second step only after the first has been accomplished.

THE SERIAL SLICE TECHNIQUE AS A BASIS FOR RECORDING DATA

There is little question as to the optimal method of making a pictorial record of the myocardium. Since serial slicing is the most accurate and thorough method available for the exploration of the muscle,[1] a set of drawings or retouched photographs of the slices themselves provides a logical and satisfactory record of the gross findings (Fig. 8). The sites of microscopic sections can be readily shown. Color photographs of any or all slices can be taken when practical. It is easy, moreover, to preserve representative slices for future reference.

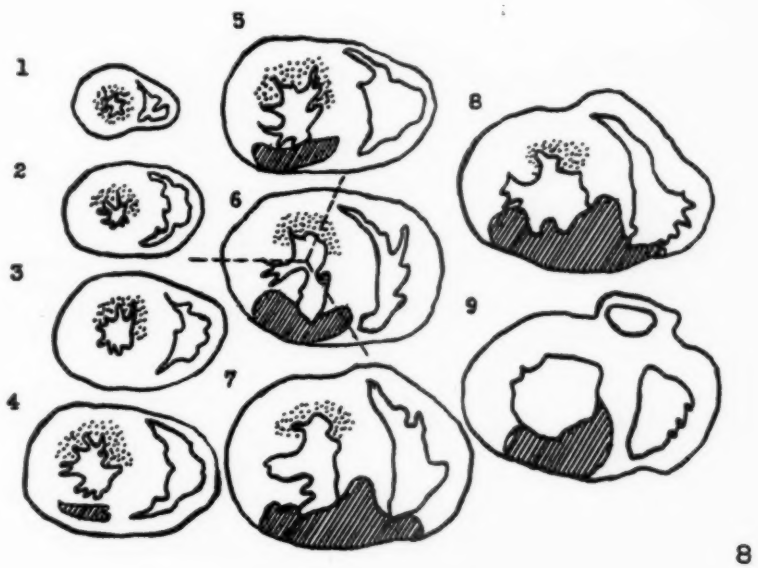


Fig. 8.—Drawing made of the slices from a heart which contains a large, recent "posterior" infarct (shaded) and an old "anterior" scar (stippled). The slices have been numbered beginning at the apex. The anterior surface of each slice is toward the top of the page and the observer views the basal aspect of each slice.

It is rather surprising that illustrations of serially sliced hearts have not been used more frequently. To our knowledge, only Lowe[12] and Kossmann and De La Chapelle[11] have used this method systematically for correlation purposes prior to our adoption of it in 1940. Since then, Myers and associates[13] have adopted serial slicing, making drawings of the gross shape of muscle lesions on roentgenograms of injected slices. With these exceptions and the case reports by Burton and associates[3] and Price and Janes,[14] serial slice illustrations have been used only in sporadic fashion to demonstrate particular points of cardiac anatomy. Their employment in this capacity goes back many years, good cross-sectional drawings of the heart being available in Tandler's

monograph (1913).[15] More recently Gross and Kugel (1933)[16] have used serial slicing to demonstrate roentgenographically the intramyocardial distribution of injected coronary arteries. The realization that the systematic use of serial slice drawings forms a superior autopsy record seems to be of recent origin.

Pictorial records based on serial slices have many advantages in addition to their completeness and precision. The ventricular anatomy is simpler and clearer in cross section than in any other way of opening the heart. The left ventricle and the septum are seen as a heavy circular ring of muscle, about equally thick everywhere save for the papillary muscles. The right ventricle appears as a thin-walled angular or crescentic structure attached to one side of the main muscle mass.

Infarcts and scars are found almost exclusively in the left ventricular-septal muscle ring, especially its inner aspect. The right ventricular walls are seldom infarcted massively and almost never alone, small extensions from predominantly left ventricular lesions being the usual finding. For purposes of coronary disease study, therefore, the main attention can be given to the left ventricle and septum, which form a structure far simpler to deal with than an entire heart. It should be noted that all the standard cardiac landmarks are seen as clearly in serial sections as in the intact or routinely opened heart.

The simplicity of their cross-sectional form makes measurement of the left ventricular and septal myocardium comparatively easy. Axial measurements, from apex to base, are provided by the slices themselves, if they have been cut in uniform fashion. For circumferential measurements, the interventricular grooves provide fixed points, clearly visible in each slice, on the left ventricular-septal muscle ring. It is convenient and logical to draw three radii on the sketches of the slices, from the center of the left ventricular cavity through each groove and the middle of the lateral wall, thus dividing the ventricle into anterolateral, posterolateral, and septal segments (Fig. 8, Slice 6). These correspond to the conventional anatomic areas of the heart and can be further subdivided as the investigator sees fit. For radial measurements, from the left ventricular cavity outward, the thick segments of the left ventricle and septal wall can be arbitrarily divided into halves, thirds, or quarters.* It will then be possible to state where any damaged area in the left ventricular and septal myocardium is in terms of axial, circumferential, and radial units. In a word, a coordinate system is set up for that muscle area where the great bulk of myocardial damage occurs. The substance of the right ventricle can be subdivided, though in a somewhat less satisfactory fashion, by use of the margo acutus as the circumferential reference point for separating the anterior and diaphragmatic regions.

In this manner damage can be recorded accurately, the anatomic relationships of the ventricular muscle mass can be clearly envisaged, and the position of any point in the heart can be stated precisely in terms of axial, circumferen-

*It is not usually practical to differentiate the layers of the wall on the basis of muscle bundles (though this could be done), because the number and arrangement of anatomic muscle layers varies in different parts of the ventricles.

tial, and radial coordinates. The only disadvantage of any autopsy report in this form is that ten or twelve pictures have to be looked at for every heart studied. The lesions, divided into parts by the slicing, have to be put together by the imagination. While such a synthesis can be made mentally for any single heart by an experienced observer, a considerable imaginative effort is required, the picture conjured up is fleeting, and it is almost impossible to make comparisons within a series of hearts.

It is therefore convenient to reconstruct the appearance of the heart as it was before it had been sliced (a simple procedure for any organ that has been serially sliced), making the muscle transparent and the myocardial lesions

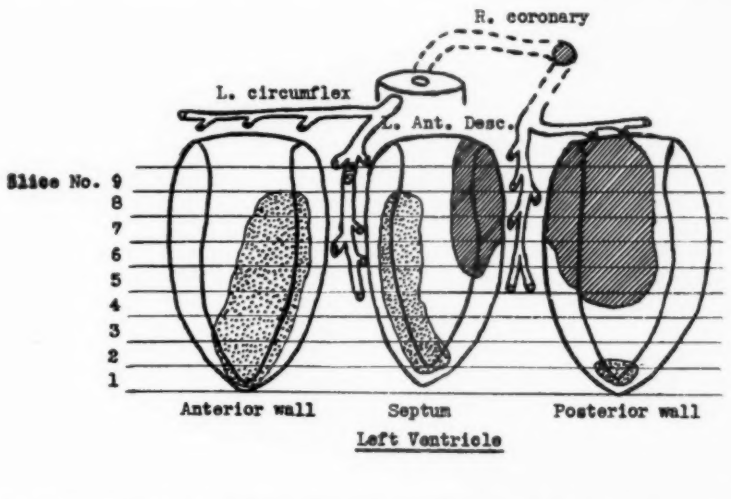


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Fig. 9.—A myocardial map of the ventricular lesions shown in Fig. 8, with coronary lesions also shown. The three segments, anterior wall, septum, and posterior wall, are depicted as if cut apart at the interventricular grooves and in the midline of the lateral wall (see Fig. 8, Slice 6). The segments are viewed from their inner aspect, the cut edges displaying the thickness of wall affected by the lesions.

The dotted portion of the right coronary artery represents its course around the base of the right ventricle (not illustrated). The recent infarct (shaded), involving the full thickness of the posterior wall and the adjacent septum, is consequent on recent thrombosis (shaded) of the right coronary artery. The old scar (stippled), affecting the subendocardial region of the apex, the anterior wall, and the left ventricular side of the septum, is related to an organized thrombus (stippled) in the left anterior descending coronary artery.

opaque. Provided such a drawing keeps clear the relation of the lesions to the coordinate system just described, an accurate transfer of data from serial slices to this or any sort of illustration is possible.

A NEW SCHEMA OF THE VENTRICLES OR MYOCARDIAL MAP

We found it best to illustrate the left ventricular-septal muscle mass as it would appear from its endocardial aspect after it had been cut open by radial incisions down the anterior interventricular groove, the posterior interventricular groove, and a line midway between them along the lateral wall, the right ventricular walls having first been cut away. Three triangular pieces of

muscle result from such a procedure: (1) an anterolateral segment bearing the anterior papillary muscle, (2) a septal segment, and (3) a posterolateral segment bearing the posterior papillary muscle.*

The myocardial map (Fig. 9) is a drawing of the appearance of these triangular segments seen from the left ventricular cavity side and placed so that their axes are parallel and their bases at the same level. A series of transverse parallel lines will then correspond to the position of the slices which actually would be used in exploring the myocardium. These constitute lines of latitude for the map. The meridians, or lines of longitude, are the anterior and posterior interventricular grooves, and the midline of the lateral wall of the ventricle. Because the walls of the left ventricle have considerable thickness, it cannot be rolled out flat and is not truly "developable" in the cartographic sense. The map consists of an isometric projection drawing of the segments rather than a flat chart. Since the left ventricular endocardial surfaces of the segments are smaller, their cut edges appear in perspective and are used to indicate the part of the wall involved. This is an important part of the record for left ventricular and septal damage.

The main epicardial rami of the coronary arteries follow the atrioventricular and interventricular grooves. As these positions are also the sites of separation of the segments in our map, these vessels may readily be added to it in schematic fashion. The proximal portion of the right coronary artery is represented diagrammatically to show how its terminal portion reaches the back of the left ventricle by passing around the tricuspid valve ring.

Data accumulated by the slicing technique and recorded by sketches of the slices can be transferred to the myocardial map with as great precision as the investigation seems to demand. On such sketches radial lines drawn from the center of the left ventricle through the anterior and posterior interventricular grooves and the center of the lateral wall divide the main portion of each slice into three segments. These, if piled on top of each other, would correspond directly to the segments of the map. The data from each slice of the myocardium are transferred to the appropriate position of each segment in the map until a reconstructed picture of the lesion is gradually built up.

It is necessary to make a slightly different muscle map for each heart if the anatomical variations in the coronary tree or localized thinning of the heart wall are to be recorded. Mural thrombi and coronary lesions are indicated in the same diagram. The precise position of microscopic sections can be shown. In hearts with multiple lesions, the age of each, as finally determined by microscopic study, is shown by appropriate color or crosshatching. Thus, the whole

*To make a demonstration specimen the dissection proceeds as follows: The auricles having been removed, the free walls of the right ventricle are clipped away close to their attachments at the interventricular grooves and the infundibular area. The remainder of the specimen, a conical chamber with a patch of right ventricle endocardium on its septal side, is opened first along the "lateral" wall, opposite the middle of the septum, and can be partially flattened out after its valve rings have been cut at their juncture. Cuts from apex to base following the course of the interventricular grooves then result in the three segments depicted in the map. The right ventricular specimens can be flattened out by cutting a few trabeculae carneae, and divided along the acute margin to form other map segments if desired.

of the relevant pathologic data may be concentrated in a single diagram, with the interrelationships between coronary and myocardial lesions and the main ventricular landmarks accurately preserved.

DISCUSSION

There is no need to construct a myocardial map in just the form we have chosen. Once lesions have been related to the system of coordinates by drawings made of the slices, a basis is established whereby any type of reconstruction desired may be effected by a purely geometrical rearrangement. The map to be used in this study, however, emphasizes the facts which have proved most fruitful in interpreting and localizing myocardial damage resulting from coronary disease, juxtaposing them so that the eye can grasp readily their most significant interrelationships. The picture of damage seen in the myocardial map is, of course, no more accurate than the record of serial slices actually used for exploring the ventricular muscle. Unlike other schematic illustrations, however, it is no less accurate than the autopsy which it epitomizes.

In the myocardial map the left ventricle is treated as if it were a conical chamber, ringlike in cross section. Its intracardiac portion, defined by radial cuts along the interventricular grooves, is the interventricular septum. Despite the fact that many workers seem to consider this as a sort of international zone, assigned to neither ventricle, there are good reasons for considering it a part of the left.

Functionally, the left ventricle might be considered as composed of all the muscle that directly aids in expelling blood through the aortic ring. Certainly most of the septum appears to take part in this action. Anatomically, the ventricular muscle bundles, in so far as they make any distinction between the chambers, have an arrangement not inconsistent with the concept of septal continuity with the left ventricular walls.* The thickness and curvature of the septum as seen in transverse section (Fig. 8) in no way suggests a passive partition between the ventricular cavities. It is further noteworthy that in hypertension and valvular disease the septum and the left ventricular walls hypertrophy together.

Aside from these reasons, regardless of their cogency, the septum must be treated as part of the left ventricle from the pathologic point of view. Infarcts and scars in the left ventricular walls run into the septum with great frequency, instead of crossing to the right ventricle. The anterior and posterior descending coronary vessels supply it not only by their high septal branches but by multiple penetrating rami throughout their length, and septal anastomoses between right and left coronaries are probably the richest in the heart.[18,19] The distribution of the coronary circulation would seem hard to understand without attention to the septal vascular bed. Moreover, the lo-

*Of the six main ventricular muscle bands, only one, the scroll (*M. Ventriculorum Circumambiens*), passes into the septum from the right ventricle. The superficial and deep sinospiral and bulbospiral muscles, in so far as they form the septum, enter it from the left ventricle and pass out of it to ramify in the left ventricle again. The longitudinal interventricular muscle starts at the base of the septum, and, having traversed its length, passes also to the left ventricle.[17]

cation of the bundle of His in the upper septum makes this a strategic area, in which the localization of myocardial damage might be expected to be of signal importance.

Clearly the septum, or intracardiac portion of the left ventricle, as one might choose to call it,* must form an important part of any diagram of the muscle and not merely an afterthought or a detached fragment; otherwise many important relationships will be destroyed. They are preserved in the type of myocardial map used in this study.

Only the major epicardial coronary branches are illustrated in the diagram. This ordinarily suffices, as it is generally agreed that coronary sclerosis is limited mainly to these larger, dissectable channels. It is our experience that myocardial damage almost always shows a close correlation with the distribution of stenosis and occlusions in the proximal portions of these larger vessels. In any unusual case, however, it is easy to adjust or amplify the map.

SUMMARY AND CONCLUSIONS

The complex data resulting from thorough exploration of the heart muscle in coronary disease present problems of recording and illustration which must be solved before a clinicopathologic correlation study of any series of patients can be accomplished. The character of the ventricular anatomy, the shape of infarcts and scars, and the defects of the standard nomenclature make verbal description of autopsy findings unsatisfactory.

The usual methods of illustration fail both as complete pictorial records of myocardial damage and as useful epitomes of the relevant pathologic facts and their important interrelationships. When hearts have been studied by a method which divides the ventricles into transverse slices, accurate drawings of the slices make excellent records.

From an adequate pictorial record, it is possible to construct a graphic representation, or myocardial map, of arterial and muscle lesions. A convenient map of the left ventricular and septal muscle is described, which permits concentration of all relevant pathologic data in a single diagram.

Combination of the serial slice method for examining and recording with the myocardial map for reconstructing, correlating, and illustrating data provides an efficient deployment of standard techniques for the localization and interpretation of muscle damage. If the possibilities of these and similar methods are more fully explored, clinical and electrocardiographic diagnoses can be placed on a much more solid footing, and the clearer understanding of the natural history of coronary disease thus gained should permit better evaluation of the results of therapy.

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*Richard Lower (1631-1690)[2] had observed: "The wall of the right ventricle is much thinner and is attached to the side of the left ventricle like some appendage; . . . describing only half a circle in its movement. . . . The septum helps the contraction of the left ventricle only . . . and, indeed, it could not be otherwise since this septum is part of the left ventricle, and its fibers are continuous everywhere with the general surface of the left ventricle and merge into it."

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THE OCCURRENCE OF PAROXYSMAL HYPERTENSION IN PATIENTS WITH INTERMITTENT CLAUDICATION

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THE syndromes of angina pectoris and of intermittent claudication are similar in that both are dependent upon the activity of ischemic muscular organs. For this reason, the classical work of Lewis[1] and of Katz,[2] designed to elucidate the mechanism of angina pectoris, was done primarily on striated muscles since the arm or leg muscles lent themselves admirably for study. Exercise of muscles experimentally rendered ischemic* gives rise to: (1) pain within the region being exercised,[3,4] (2) a marked increase in blood pressure,[5,6] and (3) tachycardia.[7] In spite of the fact that all three phenomena probably occur with the production of ischemia in muscles, only the pain element has been properly investigated.[1-4,8-12] Incidental phenomena which occur in patients with intermittent claudication deserve an explanation. For example, hypertrophy of the heart without valvular disease was found by us in such patients, even though the blood pressure was normal at rest. The fact that many of these patients die suddenly without apparent cause also requires analysis.

In order to assay the possible clinical importance of the induced rise in blood pressure and the tachycardia, we have studied the general cardiovascular reactions produced by exercise of spontaneously ischemic voluntary muscles in man. In this report, the blood pressure changes and the variations produced by several drugs following exercise of the legs in patients with intermittent claudication are described. The observations concerned with heart rate and with the origin of the pain thus produced will be reported later.[13,14] In addition, there is described a new method which permits the detection of impairment of the arterial circulation in exercising legs, even when the blood flow appears adequate at rest.

METHOD

Ten male patients, between the ages of 39 and 70 years, with intermittent claudication of the legs, were studied. Their clinical histories are summarized in Table I,*A*. The procedure described by Allen, Barker, and Hines[16] was followed, but more stress was laid on oscillometry. For the purpose of this report we will deal only with the work of the posterior muscles of the leg, although it is recognized that other muscles of the body are also involved in the effort.

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*By ischemic muscles is meant muscles with a poor or an absent arterial blood flow.

A simple device, consisting essentially of two 4-kilogram weights which could be raised separately by each foot, was employed. The weights were raised 7.0 cm. at a rate of forty times a minute and the power developed by each leg was 11.2 kilogram-meters per minute. This is derived from the equation: Power = 4.0 Kilograms × 0.07 meter × 40 times per minute.

Patients were comfortably seated in a warm room fifteen to twenty minutes before starting the experiments. Blood pressures were determined by a cuff on the right arm every fifteen to twenty seconds, and the pulse rate was simultaneously recorded from the other arm. Each patient was then instructed to perform the exercise until he experienced pain similar to that noted in walking. After a rest, during which the pain disappeared, the exercise was repeated. The experiment was begun when the blood pressures and pulse rates had been constant for three successive minutes. The legs were exercised five times, first separately

TABLE I, *A*. CLINICAL STUDY OF PATIENTS WITH INTERMITTENT CLAUDICATION

PATIENT NO.	AGE	HEART FAILURE	ANGINA PECTORIS	HEART SIZE*	ELECTROCARDIOGRAM	DIABETES MELLITUS	EYE-GROUND CHANGES†	COLD-PRESSOR TEST[15]	LOWER LIMBS‡	
									RIGHT	LEFT
1	51	Yes	No	Enlarged	Auric. fibr.	No	2	—	3	4
2	50	No	No	Normal	Normal	No	2	+	3	3
3	62	No	No	Normal	Normal	No	2	+	2	2
4	43	No	No	Enlarged	Normal	No	2	+	2	2
5	70	Yes	No	Enlarged	I-V block	No	—		2	2
6	39	No	No	Normal	Normal	No	2		2	1
7	62	No	No	Normal	Normal	No	2	+	3	3
8	45	No	No	Normal	Normal	Yes	-	+	3	2
9	50	Yes	Yes	Enlarged	C.C.I.	No	2	+	3	1
10	66	No	No	Normal	Normal	Yes	4	+	3	3

TABLE I, *B*. CLINICAL STUDY OF PATIENTS WITHOUT INTERMITTENT CLAUDICATION (CONTROLS)

PATIENT NO.	AGE	HEART FAILURE	ANGINA PECTORIS	HEART SIZE*	ELECTROCARDIOGRAM	CLINICAL DIAGNOSIS
11	42	No	No	Normal	Normal	Normal
12	20	No	No	Enlarged	L.V.P.	Coarctation of the aorta
13	16	No	No	Normal	Normal	Normal
14	66	No	No	Enlarged	L.V.P.	Rheumatic aortic stenosis
15	61	No	No	Enlarged	L.V.P.	Hypertensive heart disease

*Determined by x-ray examination.

†Classification of Wagener and Keith, Medicine **18**:317, 1939.

‡1, Normal; 2, intermittent claudication in warm extremities; 3, intermittent claudication in cold extremities; 4, intermittent claudication in cold extremities, trophic changes and/or rest pain.

C.C.I., Chronic coronary insufficiency.

Auric. fibr., Auricular fibrillation.

I-V block, Intraventricular block.

L.V.P., Left ventricular preponderance.

and then both together. A ten-minute rest period was allowed between each limb exercise. If the patient experienced no pain, two ten-minute periods were studied, with a ten-minute rest period. Finally the same exercise was performed one minute after a pressure cuff inflated to 280 mm. Hg was placed around the thigh and continued until the appearance of pain similar to that experienced without the cuff.

As controls, five patients without intermittent claudication but with other cardiovascular disease (Table I,*B*) performed the same exercises.

RESULTS

Patients With Intermittent Claudication (Figs. 1-4).—In the ten patients exercise was performed unilaterally, seventy-four times; bilaterally, forty-seven times; and after the pressure cuff was placed around the thigh, seventeen times. In patients with unilateral intermittent claudication only, the results obtained in the diseased leg will be considered.

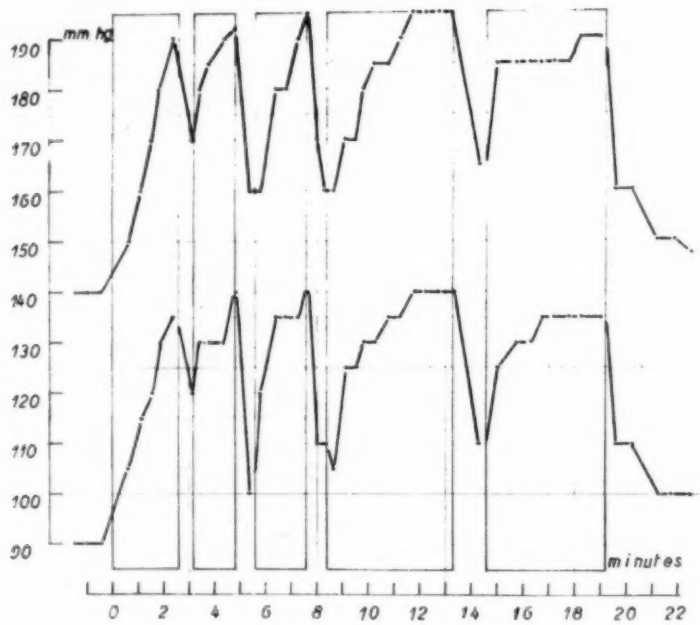

Fig. 1.—Typical experiment showing the blood pressure increases induced by unilateral leg exercise in Patient 8. The rectangles mark the exercising periods. (For method see text.) Upper line represents systolic and lower line represents diastolic pressure.

At the beginning of each exercise a sudden rise in blood pressure was observed which was sustained until the termination of the exercise; the blood pressure then returned toward the initial levels. The increase in pressure was not dependent on the development of pain, since the pressure always increased before pain appeared.

The blood pressure increases ranged between 0 and 70 mm. Hg and averaged 40 mm. systolic and 30 mm. diastolic. No significant difference in the pressure

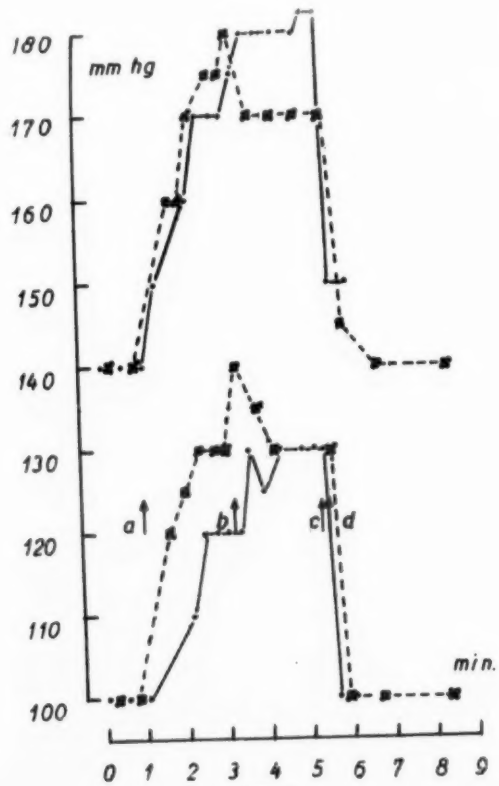

Fig. 2.

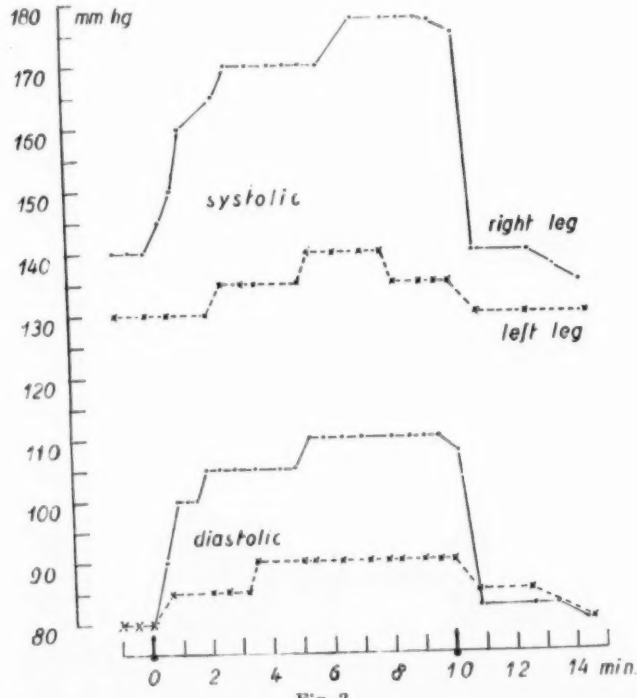

Fig. 3.

Fig. 2.—Blood pressure variations induced by leg exercise in a patient with intermittent claudication. The upper lines represent systolic and the lower lines represent diastolic blood pressure. The solid lines represent exercise without the cuff. Exercise began at *a* and continued until *d*. The dotted line represents pressure changes during exercise of the same leg, but with a cuff inflated to 280 mm. Hg placed around the thigh. Exercise in this case was performed from *a* to *b*, at which time pain forced cessation of the exercise. The pressure in the cuff was maintained until *c*. Note the great similarity between the blood pressure changes induced by both kinds of exercises (from *a* to *b*).

Fig. 3.—Blood pressure variations induced by exercise in a patient with intermittent claudication of the right leg (. ——— .). The results of exercise of the healthy left leg are also shown (x — — — x). The same exercise was performed in both instances (↑—↑).

increase was noted in patients during unilateral or bilateral exercise, with or without the induction of ischemia with the cuff. In two patients the pathologic process was unilateral. The systolic blood pressure increases brought about by the exercise of the diseased limb were between 30 and 60 mm. Hg, and the diastolic increases were between 30 and 45 mm. of mercury. The changes induced by the normal leg working under the same conditions were 5 to 20 mm. Hg systolic and 10 to 20 mm. Hg diastolic.

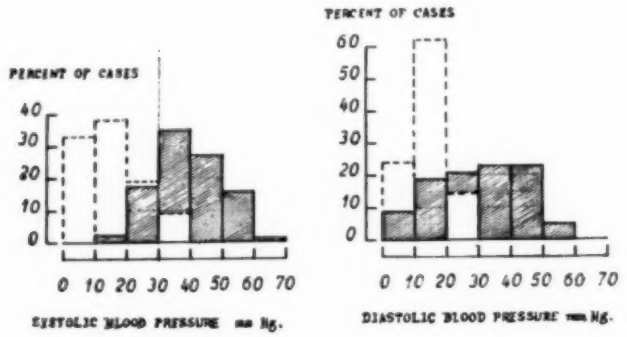

Fig. 4.—Frequency distribution of the blood pressure rises induced by the exercise of legs with intermittent claudication (solid gray rectangles), and of the legs of normal controls (dotted white rectangles).

The Ischemic Index (Fig. 5).—In order to compare the ischemia which occurs naturally with that induced artificially, the blood pressure variations induced by exercise were correlated by using the following formula:

$$I = \frac{\delta S + \delta D}{\Delta S + \Delta D}$$

in which

I = ischemic index,

δS = increase in systolic pressure during exercise without the cuff,

δD = increase in diastolic pressure during exercise without the cuff,

ΔS = increase in systolic pressure during exercise with the cuff, the exercise being continued until pain forced an end to the exercise, and

ΔD = increase in diastolic pressure during exercise with the cuff, the exercise being continued until pain forced an end to the exercise.

The ischemic index thus calculated was found to vary between 0.20 and 1.60, its mean value being 0.88 ± 0.03 and 1.01 ± 0.04 in unilateral and bilateral exercise, respectively. The difference between unilateral and bilateral exercise was not statistically significant. In 95 per cent of the cases the ischemic index was equal to or greater than 0.60.

Comment.—It is concluded that in our patients the same blood pressure variations were induced by exercising one leg, both legs together, or one leg with a

cuff that completely interrupted the arterial circulation. In other words, the same pressure increases could be induced with a partially ischemic limb (without the cuff) or with an absolutely ischemic limb (with the cuff). This finding cannot be applied to patients in whom the pathologic process was unilateral. In them, the blood pressure changes induced by exercising the healthy leg are smaller than those induced by exercising the diseased leg (Fig. 3), and the exercise of both together raises the pressure to levels similar to those induced by exercising the diseased limb alone.

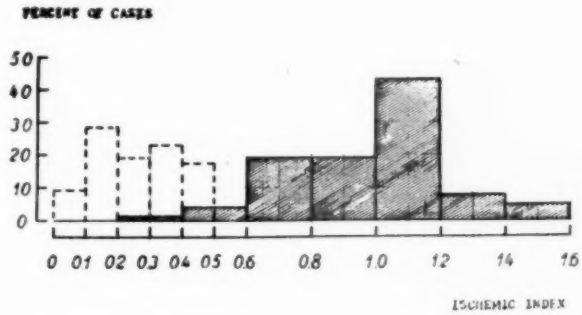

Fig. 5.—Frequency distribution of ischemic index in legs with intermittent claudication (solid gray rectangles), and in controls (dotted white rectangles).

Controls (Figs. 4 and 6).—The results obtained with the healthy leg in patients with unilateral intermittent claudication are also included here. In these seven patients, ten exercises were performed with both legs, twenty-one with one leg, and nine with one leg after the cuff was in place.

During the exercise of a nonischemic limb, the increase in blood pressure was very small, the maximum being registered from two to five minutes after the beginning of the exercise and returning toward the initial levels even before the exercise was completed. The blood pressure changes were found to lie between 0 and 40 mm. Hg, averaging 15/15 mm. Hg, regardless of whether one or both legs were exercised. The standard error of this difference[17] is for the systolic pressure $\delta = 3.28$ and for the diastolic $\delta_D = 1.53$. These differences are therefore statistically insignificant, since they are smaller than twice these standard errors. The ischemic index was found to vary between 0 and 0.49, the mean being 0.26 ± 0.02 and 0.23 ± 0.03 in unilateral and bilateral exercises, respectively.

Comment.—It is concluded that in these patients with normal circulation to the limb, the same increase in blood pressure was produced by the exercise of one or of both legs, but greater differences were obtained when the exercise was performed under artificially induced ischemic conditions. Furthermore, it was generally found that the blood pressure fell toward normal even before the exercise was finished, although this never occurred in subjects with ischemic limbs. It is true that in subjects whose limbs were ischemic the exercising periods were shorter. The standard errors of the difference between the ischemic control and the nonischemic control limbs were 2.40 and 1.70 in the systolic and diastolic

pressures, respectively. As the difference between the means was much greater than twice these standard errors, the said difference is statistically significant.

The "ischemic index," which is easily determined, provides a valuable means for determining whether the arterial blood supply to the limb is adequate. It was found to be greater than 0.60 in 95 per cent of the patients with intermittent claudication and less than 0.50 in the patients without intermittent claudication.

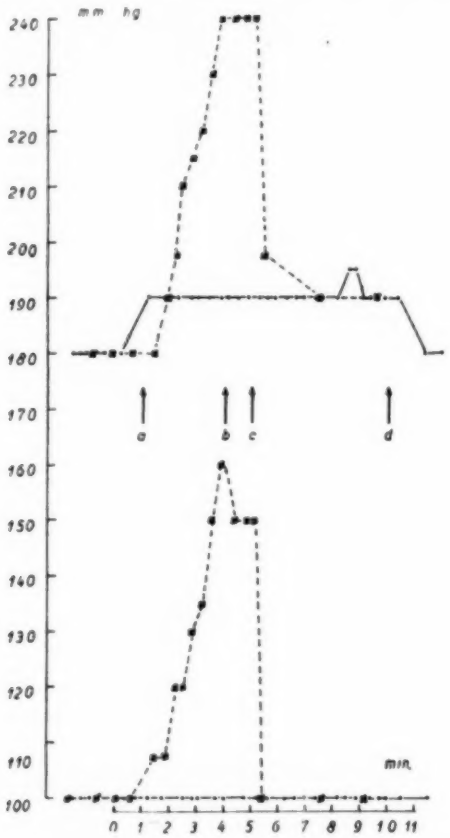

Fig. 6.—Blood pressure variations induced by leg exercise in a patient without intermittent claudication. This patient had coarctation of the aorta, but the arterial circulation in his legs was normal. The solid line represents systolic and diastolic blood pressures during exercise of the left leg without the cuff. The dotted line shows blood pressure during exercise of the same leg, but with a cuff inflated at 280 mm. Hg placed around the thigh. At *a* the same exercise was begun in both instances. In the experiment with the cuff (dotted lines) the exercise was stopped at *b*, but the cuff pressure was not released until *c*. In the experiment without the cuff, exercise began at *a* and continued until *d*. Note the great difference in blood pressure between the two experiments.

The Effect of Drugs on the Blood Pressure Rise in Patients With Intermittent Claudication.—In order to assay the mechanism of the pressor reaction, nitrites and tetraethyl ammonium chloride were used.

A. *Vasodilator Drugs* (Table II).—Nitrites, some with rapid action (nitroglycerine) and some with more prolonged effects (Mannitol hexanitrate), were given orally. In six patients, twenty-seven experiments were done five minutes

after the sublingual administration of four drops of an alcoholic nitroglycerine solution. As it was found that no differences existed between the pressor reaction induced by exercising one or both legs, these experiments will be jointly reported here. In five patients, the increases were smaller than when no nitroglycerine was administered; the systolic mean in all six patients was 23 ± 2 and the diastolic was 24 ± 3 mm. of mercury. The ischemic index was within normal limits in five patients and remained abnormally elevated in only one.

TABLE II. BLOOD PRESSURE VARIATIONS INDUCED BY LEG EXERCISE IN PATIENTS WITH INTERMITTENT CLAUDICATION, FOLLOWING THE ADMINISTRATION OF VASODILATOR DRUGS

INCREASE IN PRESSURE (MM. HG)	NUMBER OF OBSERVATIONS*			
	NITROGLYCERINE		MANNITOL HEXANITRATE	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
0–9	2	4	1	2
10–19	10	9	1	8
20–29	8	3	7	1
30–39	5	7	2	2
40–49	1	3	0	0
50–59	1	1	1	0
60–69	0	0	1	0
Total observations	27	27	13	13
Mean increase (in mm. Hg)	23	24	29	15
Standard error	±2	±3	±4	±2
Standard deviation	10	14	16	8

*Exercise of one or both legs is jointly reported here.

In two patients, the exercise was performed after the cuff inflated to a pressure of 280 mm. Hg was placed around the thigh. The blood pressure reactions in this case were similar to those produced without the nitroglycerine, the ischemic index being 0.93 and 1.28, respectively.

In four patients, thirteen bilateral exercises were performed one hour following the administration of Mannitol hexanitrate. The blood pressure changes were similar to those obtained without the drug, and in only six patients was the ischemic index found to be within normal limits.

It is concluded that nitroglycerine, a rapidly acting vasodilator, prevented the pressor reaction induced by the exercise of naturally occurring ischemic limbs, while Mannitol hexanitrate was only partially effective. Furthermore, the fact that nitroglycerine did not prevent the pressor reaction elicited after placing of the cuff suggests the presence of vascular spasm in some of these patients during exercise.

B. *Tetraethylammonium Chloride* (Table III).—In four patients, 0.7 to 1.2 Gm. of tetraethylammonium chloride were given intramuscularly one hour before the experiments. Fourteen experiments were performed with one leg, without the cuff, and four with one leg after the cuff was in place.

TABLE III. BLOOD PRESSURE VARIATIONS INDUCED BY LEG EXERCISE IN PATIENTS WITH INTERMITTENT CLAUDICATION, FOLLOWING THE ADMINISTRATION OF TETRAETHYLAMMONIUM CHLORIDE (TEA)

INCREASE IN PRESSURE (MM. HG)	NUMBER OF OBSERVATIONS			
	EXERCISE ONE LEG			
	WITHOUT CUFF		WITH CUFF	
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
0–9	1	1	0	0
10–19	6	7	1	1
20–29	5	4	1	1
30–39	1	1	1	1
40–49	0	1	0	1
50–59	0	0	1	0
60–69	1	0	0	0
Total observations	14	14	4	4
Mean increase (in mm. Hg)	22	20	32	30
Standard error	±4	±3	±6	±7
Standard deviation	14	10	11	13

In the exercise without the cuff, the increases ranged between 0 and 60 mm. Hg, with a systolic mean of 22 ± 4 and a diastolic mean of 20 ± 3 mm. of mercury. In the exercise with the cuff, the increases lay between 10 and 50 mm. Hg, with a systolic mean of 32 ± 6 and a diastolic mean of 30 ± 6 mm. of mercury. The ischemic index was less than 0.60 in ten cases.

It is concluded that although tetraethylammonium chloride blocks the autonomic ganglia, it did not suppress the pressor reaction of the exercise in our patients.

DISCUSSION

The values given by us for the blood pressure changes induced by the exercise in our control patients are different from those given by other authors for normal subjects.[18-21] The apparent discrepancy can be accounted for by the differences in the methods employed, since the blood pressure changes are determined by the amount, the degree, and the duration of the exercise,[22] being proportional, but not linearly so, to the work performed.[21] In our experience, similar blood pressure changes were induced with exercise of one or of both legs despite the fact that the work performed with two legs was twice as much as that performed with a single leg. The importance of recording the blood pressure *during* the exercise cannot be overemphasized, since the pressure rapidly returns to normal as soon as the exercise is stopped.[20,24] In the majority of the control patients, the blood pressure tended to decrease after eight to ten minutes even though the exercise was continued. Similar observations have been reported by others.[18,19] In contrast,

in our patients with intermittent claudication the hypertension was sustained during the entire exercising period. Postexertional hypotension was not seen by us, although this has been observed by others.[25]

The effect of exercise of ischemic muscles has been studied clinically mainly from the point of view of the elicited pain,[1-4,8-12] but few have investigated the arterial hypertension and tachycardia which occur coincidentally. Reid[5] mentioned this fact, and Alam and Smirk[6,7,26-28] and Malinow and his associates[29] made a nonstatistical study in patients without apparent arterial lesions. The hypertension induced by the exercise of ischemic muscles may belong to the "nutritive reflexes" of Hess,[30] which bring about an increase of blood pressure whenever an obstruction to the blood flow appears. This mechanism may be related to the rise in pressure brought about by ischemia of the kidney,[31] of the uterus of pregnant dogs,[32] of the heart,[33,34] and by coarctation of the aorta and by the arterial injection of embolizing powder.[35]

The physiopathology of pain in intermittent claudication has been exhaustively studied by Lewis[1] and by Katz,[2] and its clinicopathologic basis established mainly by Veal[36] and by Hines and Barker.[37] Nevertheless, the generalized blood pressure variations induced in patients with claudication by exercise of the legs have not been previously reported. Blood pressure changes similar to those described by us are mentioned by Thacker[25] during the exercise of hypertensive patients and may be induced by other mechanisms (emotions, cold, and so forth). Contrary to the findings of Alam and Smirk,[28] Hines[38] and Levy and associates[39] reported that marked blood pressure increases occur more often in subjects with a tendency to sustained hypertension; and Moschcowitz[40] and many others[41,42] have stressed the role of hypertension in the production of arteriosclerosis. In our patients, great blood pressure variations were induced by exercise of the legs. While we cannot prove the importance of this mechanism in the development of hypertension or arteriosclerosis, there can be little doubt that these blood pressure changes must react unfavorably upon a previously damaged heart. In this connection, we should mention the coincidence of angina pectoris and intermittent claudication in Case 9.

The mechanism which we have reported may explain cardiac enlargement of unknown etiology in some patients. This is the case, we believe, in our 40-year-old patient (Case 8) without valvular lesions, with a normal electrocardiogram, and with x-ray signs of left ventricular enlargement. In this patient, while the resting blood pressure was 140/100 and 140/90, after a few seconds of leg exercise it increased to 190/140 (Fig. 1).

Sudden death is common in patients with intermittent claudication, but its cause has not been established.[37] The mechanism discussed in the present report, by producing repeated and sudden hypertension, may lead to cardiac or cerebral accidents in these patients. The mechanism of heart failure in patients with anemia or with generalized anoxia may also be related to the production of a rise in pressure on effort, with the resulting increased load on the heart.[43,44] A pressor reaction in exercising ischemic muscles, without the occurrence of pain, was observed by us and will be reported elsewhere.[14] In patients with angina pectoris, Levine[33] and Rosenbaum and associates[34] did not find a relationship between

pain and arterial hypertension. Our experience favors the same view, because (1) in some patients it was possible to obtain the pressor response without the occurrence of pain; (2) we frequently observed a decrease in blood pressure during the ischemic postexertional period, even in the face of persistent or increasing pain; and (3) tetraethylammonium chloride may suppress pain without completely abolishing the pressor response.

Although the hypertension was not abolished by tetraethylammonium chloride, there can be little doubt that it operates through a neurogenic mechanism.[26] This failure was due, probably, to incomplete block of the autonomic nervous system.[45-47] A direct effect of an increased venous return can be eliminated in the pressor response brought about by the exercise of limbs with a cuff inflated at 280 mm. Hg and placed around the thigh. Our observations concerning the eradication of pain are in accord with what has been reported in cases of myocardial infarction,[48] in which pain is abolished in spite of the arterial hypotension occurring coincidentally with a probably secondary decrease in coronary flow.

Manifold procedures have been described in the clinical and instrumental study of vascular disorders in the limbs,[16,49-55] but none of these measures the generalized reactions produced by the exercise of ischemic extremities. Our method is of value because it is simple and permits an easy recognition of ischemia during the exercise, a condition that occasionally may not be present at rest.

Vascular spasm has been repeatedly reported in patients with intermittent claudication.[56-63] Our observations with nitroglycerine may support this view. We have found vasodilators to be of value in partially relieving the pressor reaction in intermittent claudication, and the local conditions may thereby be improved. The fact that vasodilators are not mentioned,[64-67] or only incidentally mentioned,[68] in this connection, is due to the fact that the subjective phenomena are generally relieved in only a few cases.

CONCLUSIONS

In spite of the small number of observations, the following conclusions are tentatively offered:

1. The arterial hypertension induced by a standardized exercise of the legs in patients with intermittent claudication is much greater than that which occurs in patients without intermittent claudication. This hypertension, presumably also present while the patient is walking, represents a mechanism of repeated strain on the heart and may possibly be a determining factor in the production of arterial hypertension and/or arteriosclerosis, cardiac enlargement, and sudden death.

2. An ischemic index was found by comparison of the blood pressure changes induced by the aforementioned standardized exercises, before and after a pressure cuff inflated at 280 mm. Hg was placed around the thigh. This index was less than 0.50 in the control patients and greater than 0.60 in 95 per cent of the patients with intermittent claudication.

3. The pain experienced by these patients is apparently not the cause of the pressor response.

4. In spite of its accepted neurogenic mechanism, the pressor response was not completely abolished by tetraethylammonium chloride. In some patients it was partly abolished by vasodilator drugs, suggesting the presence of vascular spasm. The last-mentioned fact suggests that nitrites may be of value in the treatment of patients with intermittent claudication of the legs.

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THE ROLE OF ANEMIA IN THE EXPERIMENTAL PRODUCTION OF HEART BLOCK AND AURICULAR FIBRILLATION IN THE DOG

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TWO factors seem principally involved in the pathogenesis of auricular fibrillation in man and animals. The role of the vagus in the experimental production of auricular fibrillation has been established by numerous observers. Auricular fibrillation has been produced in animals and in man by the injection of parasympathomimetic substances, and in the dog by the simultaneous electrical stimulation of the vagus nerves and the auricles faradically. The second important etiological factor is anoxia of the heart. In the department from which this paper comes, Schlichter,[1] who has recently observed the development of auricular fibrillation in certain cases of anemia in man and its disappearance after transfusion, has emphasized the importance of anemia. The present investigation was undertaken in an attempt to evaluate further the role of anemia in the production of cardiac conduction disturbances as well as auricular fibrillation.

METHODS

A total of thirty-three dogs was employed in this study. Twenty-seven experiments with anemia, involving twenty-one dogs, were successfully completed. In seventeen experiments the dogs were anesthetized with Nembutal (25 mg. per kilogram), and in ten experiments unanesthetized trained dogs were used. Examination of the results with anesthetized and unanesthetized dogs revealed little difference in the reactions obtained. Standardization procedures conducted before and after anesthesia revealed little difference in the minimal standardizing dose of acetylcholine required.

Anemia was produced by three separate methods. Five animals were used twice each for the induction of anemia by different methods, and in one animal anemia was induced twice by the same method. In thirteen experiments in twelve dogs, anemia was produced by acetylphenylhydrazine given intramuscularly in dosage of 60 to 125 mg. per kilogram, divided into three daily doses. Eight dogs were made anemic by being fed *n*-propyl disulfide, 1.0 c.c. daily for four to six days. In six experiments anemia was produced by daily puncture of

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the femoral artery and removal of blood by means of a vacuum bottle. Hemoglobin determinations were made by the photocolorimetric method at the time of standardization procedures.*

Acetylcholine chloride† was employed for the production of cardiac arrhythmias. The drug was dissolved in distilled water in concentrations of 0.1 mg. per cubic centimeter, 1.0 mg. per cubic centimeter, and 10.0 mg. per cubic centimeter, and injected into the right foreleg vein of the dog. Injections were always made into the same area of the vein in order to eliminate differences in circulation time. Electrocardiographic tracings were taken by means of a direct-writing electrocardiograph (Viso-Cardiette). Varying amounts of acetylcholine in volumes not larger than 1.0 c.c. were injected as rapidly as possible with a tuberculin syringe and a No. 23 needle until the minimal dose which would produce second degree A-V block was determined. At least three minutes were allowed to elapse between successive injections. In most instances a single blocked-out ventricular beat constituted the response to the minimal dose. In all instances, before the establishment of the minimal dose, a slightly smaller dose was injected at least twice, and shown to be incapable of producing second degree A-V block. After the establishment of the minimal dose,‡ doses of ten and twenty times this amount were injected. The standardization procedure was repeated two and occasionally three times on different days, the intervals varying from days to weeks. After the animals had been properly standardized, anemia was produced by the methods described and the standardizations were repeated with the animals at various levels of anemia, both in the stage of increasing anemia and in the recovery stage.

RESULTS

1. *Minimal Standardizing Dose of Acetylcholine.*—It was found that the control minimal standardizing dose necessary to produce second degree A-V block showed wide variability among different animals, ranging from 0.08 mg. to 3.0 mg. of acetylcholine. However, the control minimal standardizing dose for any individual animal remained relatively constant even when the determinations were separated by many weeks. This is well illustrated in Table V. The minimal standardizing dose did not appear to be related to the weight or sex of the animals, but did show a crude relationship to the animals' initial hemoglobin levels (Fig. 1). A given weight of acetylcholine produced a similar effect regardless of the dilution of the solution employed. This constancy of response to acetylcholine provided us with a base line for the determination of changes in sensitivity to the production of A-V block and auricular fibrillation. Anemia produced by any of the three methods employed resulted in increased sensitivity of the animals to acetylcholine. Block and auricular fibrillation were produced by doses of acetylcholine much smaller than those required in the pre-anemia

*We are indebted to Dr. K. Singer, Hematology Department, for his kindness in permitting us to use his photocolorimeter.

†We are indebted to Hoffmann-LaRoche, Inc., for the generous supply of this drug.

‡Henceforth referred to as the "minimal standardizing dose."

standardizations. After the animals had recovered from the anemia, the minimal standardizing dose returned in most instances to levels comparable with the pre-anemia standardizations.

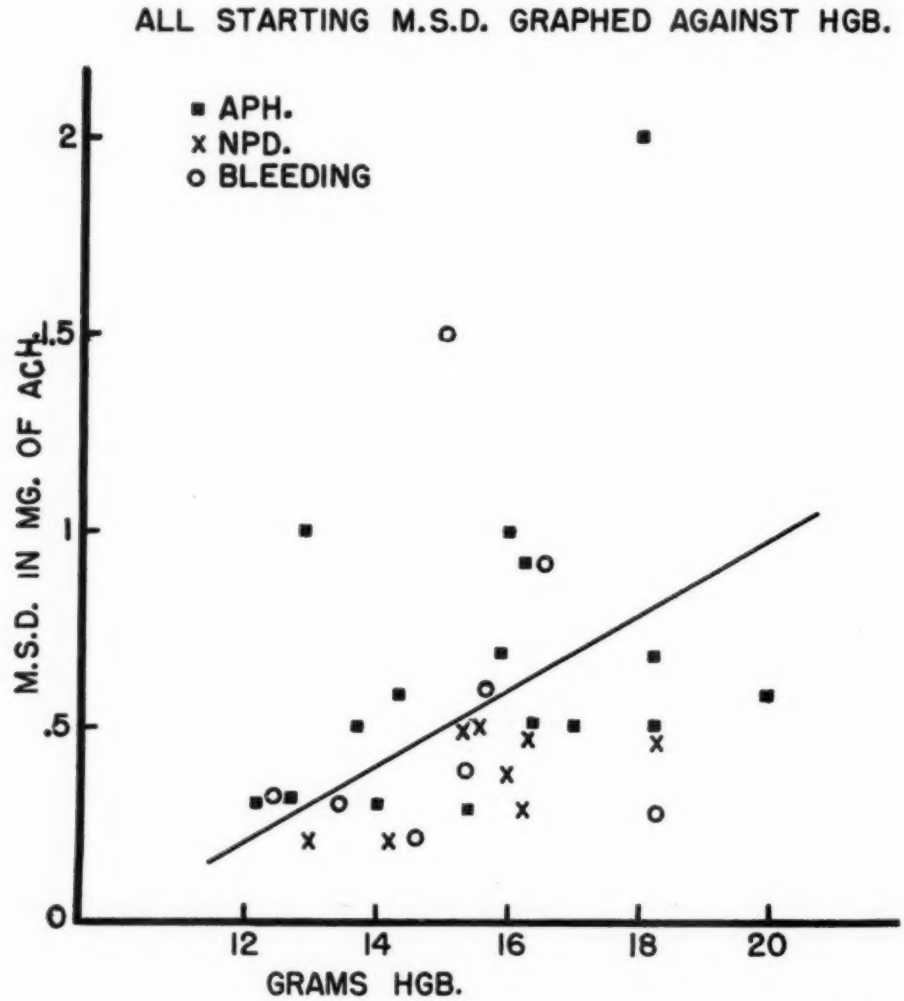

Fig. 1.—Relation between starting minimal standardizing dose (*M.S.D.*) of acetylcholine and hemoglobin content (Hgb) of blood. *APH* = acetylphenylhydrazine dogs; *NPD* = *n*-propyl disulfide dogs; *bleeding* = dogs in which hemorrhagic anemia was produced: *ACH.* = acetylcholine.

2. *Effects of Acetylphenylhydrazine (APH) Anemia.*—Thirteen experiments (in twelve dogs) were performed. One dog was used twice with a six-month intervening period. The first evidence of a fall in hemoglobin occurred on the day following the first injection of acetylphenylhydrazine. During the next two days, when this drug was still being given, continued small falls in hemoglobin occurred. Between the third and tenth day following the initial injection there was a precipitous fall in the hemoglobin level, the low point being reached within

three to seven days of the third injection. In some animals the fall in hemoglobin continued and the animal died. With the doses of acetylphenylhydrazine employed by us the low point of hemoglobin appeared to be in the neighborhood of 9.0 grams per cent. The animals which subsequently recovered attained normal hemoglobin levels in two to four weeks after the low point had been reached. In every instance in which anemia was produced by this method, the animals became markedly sensitive to the production of heart block, with the minimal standardizing dose falling to levels of approximately 10 per cent of the control values. Sensitivity was greatest when the anemia was most marked. In those animals which were followed closely during the early stages of the de-

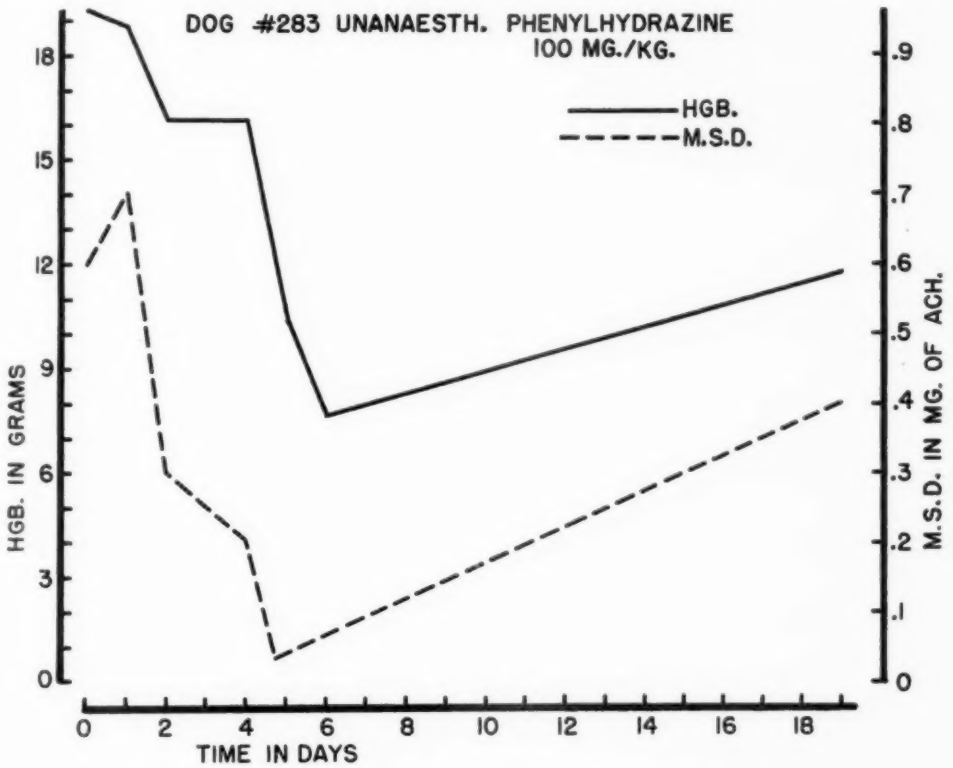

Fig. 2.—Typical experiment with phenylhydrazine. Symbols as in Fig. 1.

veloping anemia, it could be seen that within twenty-four hours after the injection of the initial dose of acetylphenylhydrazine, sensitivity began to increase considerably, although the hemoglobin levels had fallen only slightly. Sensitivity continued to increase with the fall in the hemoglobin levels and reached its maximum at the lowest hemoglobin levels. As the animals were allowed to recover from the anemia, the sensitivity decreased and the minimal standardizing dose eventually returned to levels approximating those of the control values. Fig. 2 shows the parallelism between the hemoglobin levels and the minimal standardizing dose in a representative dog. Results obtained in all dogs treated with acetylphenylhydrazine and surviving sufficiently long are tabulated in Table I.

TABLE I. THE MINIMAL STANDARDIZING DOSE (MSD) OF ACETYLCHOLINE BEFORE AND AFTER ACETYLPHENYLHYDRAZINE (APH) ANEMIA

DOG NO.	BEFORE APH		AFTER APH	
	HGB. (GM.)	MSD (MG.)	HGB. (GM.)	MSD (MG.)
0362	14.3	0.5 0.6 0.6	5.7 13.0	0.09 0.6
9268	 18.1	2.0 2.5	4.4 11.1	0.2 1.0
9753	 12.7	0.4 1.0 1.0 0.9	5.7 8.1 14.2	0.1 0.5 0.7
9121	 16.3	0.9 0.9	5.6 14.7 16.7	0.05 0.6 0.4
202	 18.2	0.4 0.5	16.8 9.4 5.3 8.8 11.2	0.1 0.1 0.05 0.3 0.5
196	 14.0	0.3 0.3	11.1 6.6 6.1 13.4	0.1 0.02 0.05 0.2
165	 15.9	0.7 0.6	5.1 12.3 13.8	0.1 0.7 0.2
9843	12.2	0.3	9.5 15.6	0.1 0.5
0347	 14.6	0.2 0.2	5.5 4.0	0.02 0.01
0362	 18.2	0.7	16.6 14.5 13.1 4.6	0.7 0.4 0.2 0.06
283	19.9* 15.4*	0.6 0.2 0.4	19.4 16.3 16.3 7.8 11.6	0.7 0.5 0.3 0.2 0.05 0.4

Hgb. = hemoglobin.
*Values from a previous experiment. See Table II.

3. *Effects of Hemorrhagic Anemia.*—Six dogs were standardized for this procedure. Usually a marked anemia was produced in three to five days. All six dogs were followed into the anemic phase, and there was a definite increase

in sensitivity to acetylcholine as judged by the development of second degree A-V block. Two dogs were maintained in a severely anemic state for approximately two weeks, and continued during this period to display a marked sensitivity to the development of A-V block. In the four dogs which recovered completely from the anemia, as the hemoglobin values rose there was a decline of the sensitivity toward pre-anemia levels. The sensitivity which developed during the hemorrhagic anemia was at its peak when the anemia was most severe. The sensitivity was not, however, so great as that which developed following the use of acetylphenylhydrazine. Results of the experiments with hemorrhage are summarized in Table II, and a representative curve is shown in Fig. 3.

TABLE II. THE MINIMAL STANDARDIZING DOSE (MSD) OF ACETYLCHOLINE BEFORE AND AFTER HEMORRHAGIC ANEMIA

DOG NO.	BEFORE HEMORRHAGE		AFTER HEMORRHAGE	
	HGB. (GM.)	MSD (MG.)	HGB. (GM.)	MSD (MG.)
282		0.3	9.5	0.2
	13.5	0.3		0.1
			6.3	0.1
202	18.2	0.3	10.4	0.05
	18.2*	0.4		
	18.2	0.5		
9753	16.8	0.9	10.5	0.15
	12.7*	1.0	8.4	0.20
		1.0	7.0	0.08
		0.9	4.9	0.15
			7.1	0.15
			7.0	0.1
			11.2	0.5
			12.4	0.6
0490	12.5	0.3	5.5	0.05
	16.4*	0.3	7.1	0.09
			5.8	0.07
			8.4	0.2
			10.2	0.1
267		1.0	10.3	0.8
		1.5	7.5	0.4
	14.9	2.0	8.6	0.4
			6.3	0.4
			7.0	0.5
			12.4	1.0
283		0.2	12.7	0.2
	15.4	0.4	9.5	0.2
			6.3	0.075
			8.8	0.1
			7.9	0.2
			11.9	0.5

Hgb. = hemoglobin.

*Values from a previous experiment. See Table I.

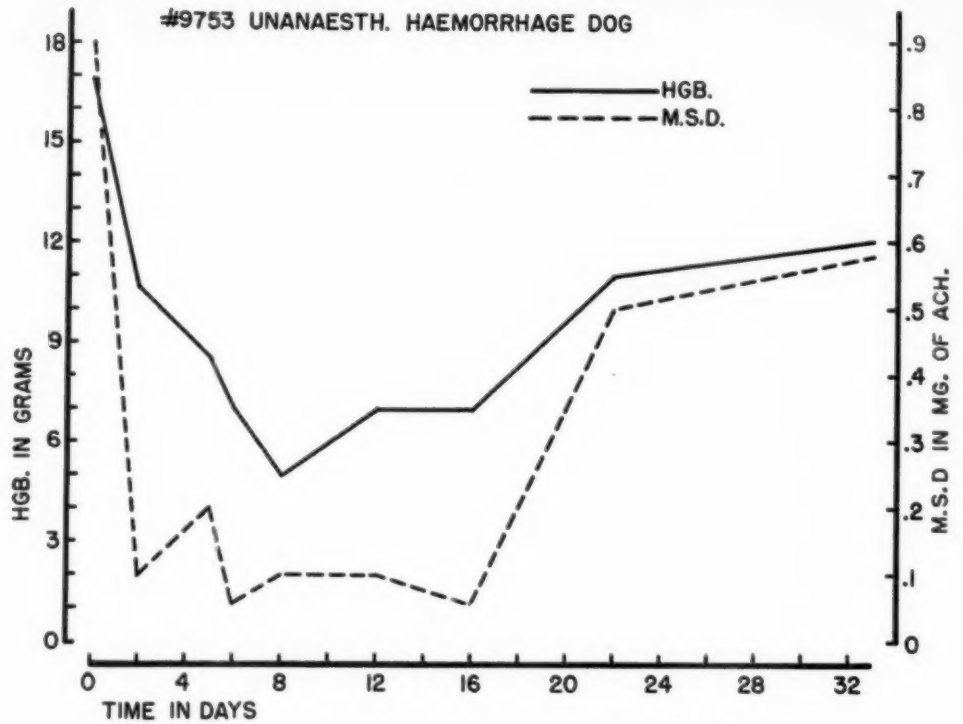

Fig. 3.—Typical experiment with hemorrhage. Symbols as in Fig. 1.

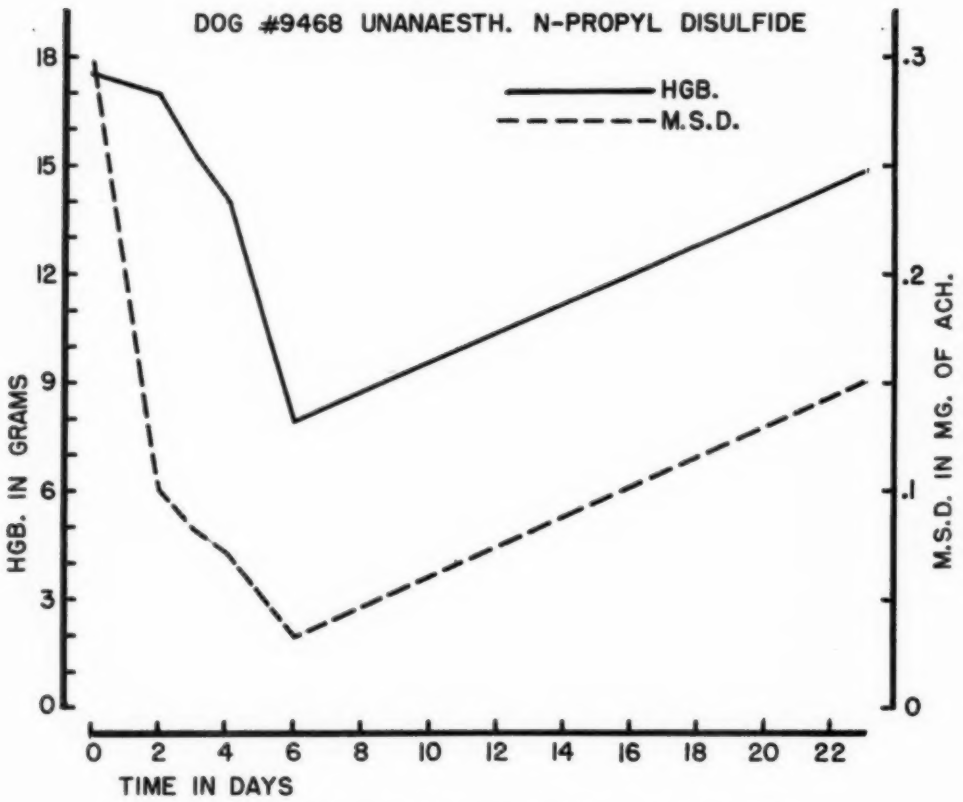

Fig. 4.—Typical experiment with *n*-propyl disulfide. Symbols as in Fig. 1.

4. *Effects of n-Propyl Disulfide Anemia.*—Eight dogs were standardized for this procedure. Five dogs showed a lowered minimal standardizing dose when assayed with acetylcholine during the anemic phase. As in the other types of anemia, the maximum sensitivity occurred at the lowest hemoglobin levels. The order of increased sensitivity during this anemia was about five times, as compared with ten times following acetylphenylhydrazine. A representative positive response in one animal is shown in Fig. 4, and the results in all animals are tabulated in Table III.

TABLE III. THE MINIMAL STANDARDIZING DOSE (MSD) OF ACETYLCHOLINE IN PRODUCING AURICULAR FIBRILLATION BEFORE AND AFTER *n*-PROPYL DISULFIDE (NPD) ANEMIA

DOG NO.	BEFORE NPD		AFTER NPD	
	HGB. (GM.)	MSD (MG.)	HGB. (GM.)	MSD (MG.)
0489		0.4	7.1	0.1
	13.2	0.4	4.6	0.3
	15.4	0.5	4.6	0.3
				0.4
			6.6	0.4
			10.1	0.8
0490	16.4	0.3	6.6	0.2
	12.5*	0.3	6.9	0.2
0454	18.3	0.5	9.5	0.2
	16.7	0.2	6.6	0.2
	16.7	0.3	8.5	0.2
			8.7	0.3
			10.6	0.3
9468	17.4	3.0	16.7	0.1
	18.1	2.0	15.1	0.8
			14.0	0.7
	18.1	2.5	7.9	0.2
0607		0.4	4.9	0.08
	16.1	0.4		
		0.3	13.0	0.4
0612		0.5	8.4	0.1
	16.1	0.4	15.0	0.5
0603		0.2	4.2	0.05
		0.1	12.2	0.1
	13.0	0.2		
0619		0.3	7.9	0.08
	15.3	0.9	13.7	0.3
		0.5		

Hgb. = hemoglobin.
*Values from a previous experiment. See Table II.

5. *Auricular Fibrillation.*—We observed a marked individual variation among dogs with respect to the ease with which auricular fibrillation could be induced by acetylcholine. Fifty per cent of all dogs tested fibrillated at some time or other in the pre-anemic stage. Our results are condensed in Table IV,

TABLE IV. INCREASED TENDENCY TO AURICULAR FIBRILLATION DURING ANEMIA

GROUP	APH	HEM	NPD
Never fibrillated	6(4)	3(1)	2(1)
Occasionally fibrillated	4(2)	2(2)	4(1)
Consistently fibrillated	2(0)	1(0)	2(2)

APH = acetylphenylhydrazine anemia.
HEM = hemorrhagic anemia.
NPD = *n*-propyl disulfide anemia.
Figures outside parentheses show the number of animals in the group; figures in parentheses show the number of animals which showed increased tendency to fibrillation of auricles after development of anemia, or which required less acetylcholine to lead to auricular fibrillation.

in which the animals carried completely through all phases of the anemias are divided into three groups according to whether the animal in the pre-anemic state (a) never fibrillated, (b) occasionally fibrillated, or (c) consistently fibrillated. The numbers enclosed within parentheses indicate the number of animals in the same group, which, after the induction of anemia, showed an increased tendency to fibrillate, fibrillation developing either more frequently or with smaller doses of acetylcholine. As can be seen, of eleven dogs which had never fibrillated before anemia, six fibrillated during the anemic phase. While the sensitization to fibrillation is difficult to discern in some animals because of the absence of a minimal fibrillating dose, it is clear and unmistakable in others. A record of one of the latter animals is shown in Table V. It should be clearly realized that

TABLE V. RELATION OF MINIMAL STANDARDIZING DOSE OF ACETYLCHOLINE REQUIRED TO PRODUCE AURICULAR FIBRILLATION TO HEMOGLOBIN CONTENT OF BLOOD IN A TYPICAL EXPERIMENT

DATE	HGB. (GM.)	MSD (MG.)
2/28/48		0.3
3/ 5/48	15.2	0.3
3/19/48		0.4
3/26/48		0.4
4/ 9/48		0.5
5/11/48		0.3
5/15/48		0.4
5/20/48	14.1	0.3
6/ 4/48	6.2	0.1
6/ 7/48	4.2	0.02
6/ 9/48	3.0	0.02

Hgb. = hemoglobin.
MSD = minimal standardizing dose.

there is no minimal dose of acetylcholine which can properly be called a "minimal fibrillating dose," since the production of fibrillation is largely dependent upon the location and timing of the initial impulse leading into fibrillation. It follows, therefore, that fibrillation may follow the administration of a given dose of acetylcholine but shortly thereafter may not follow the administration of the same or a larger dose.

6. *Relationship Between Supraventricular Block and the Development of Auricular Fibrillation.*—When electrocardiographic records showing the development of auricular fibrillation were examined, in almost all cases it was found that a P wave blocked from transmission to the ventricles immediately preceded the onset of the fibrillatory waves and seemed to initiate them. This phenomenon appears in other published tracings[2-5] but has been insufficiently emphasized except by two groups of authors.[4,5] In many of our tracings in which there was A-V block, there were P waves of unusual contour during the period of block. These P waves may be described as "double P waves" or polyphasic auricular waves. On a number of occasions it was these peculiar auricular waves which led into the typical *f* waves of auricular fibrillation. These multiple auricular waves probably represent re-entry within the auricles of an impulse arising in the sinus node or the auricles. We are in accord, therefore, with the previous deduction on this point reported from this department.[5]

7. *Relationship of Dose of Acetylcholine to the Length of Auricular Fibrillation.*—In dogs which fibrillated consistently, we observed a crude relationship between the dose of acetylcholine administered on a given day, and the length of time during which the auricles fibrillated following that dose. The figures listed in Table VI illustrate this relationship and show that with increasing doses

TABLE VI. RELATIONSHIP OF DOSE OF ACETYLCHOLINE TO DURATION OF AURICULAR FIBRILLATION IN THREE REPRESENTATIVE DOGS

DOG NO.	HGB. (GM.)	ACETYLCHOLINE (MG.)	DURATION OF AURICULAR FIBRILLATION (SECONDS)
9753	7.0	0.8	29
		1.6	53
	7.1	1.5	19
		3.0	100
	7.0	1.0	36
		2.0	99
0489	13.2	4.0	33
		8.0	84
	15.4	5.0	48
		10.0	49
	7.1	0.1	27
		1.0	40
		2.0	60
	4.6	3.0	90
		6.0	116
	4.6	3.0	44
		6.0	56
	6.6	4.0	29
		8.0	40
	14.2	5.0	30
		10.0	27
9810	14.3	0.2	17
		0.4	22
		2.0	32
		4.0	48
		6.0	3
		6.0	76
	14.3	0.5	23
		1.0	44
		2.0	145

Hgb. = hemoglobin.

of acetylcholine there is increased length of the period of fibrillation. There was a similar relationship between the dose of acetylcholine and the length of time during which the A-V block persisted. This latter relationship, which was clear when no fibrillation was seen, could also be observed when auricular fibrillation was present. In all cases where auricular fibrillation was produced, the high grade of block initially produced was manifested by a slow ventricular rate at the onset of fibrillation. As the period of fibrillation progressed, the ventricular rate increased markedly, indicating a lessening and disappearance of the A-V block. To investigate this relationship in greater detail we used an intravenous infusion of acetylcholine, in three instances, to produce and maintain auricular fibrillation over long periods of time. We observed that once auricular fibrillation was initiated, we could control the rate of transmission of impulses from auricles to ventricles by increasing or decreasing the rate of flow of the infusion. Data on such an experiment are presented in Table VII. It is clear that with higher rates of flow the ventricular rate was definitely depressed. In such a preparation, if the rate of flow of the infusion is slowed below a certain critical level for the animal, auricular fibrillation will cease after a variable period and give way to sinus rhythm. Auricular fibrillation can be reinitiated by once again speeding up the rate of the infusion. We have observed auricular fibrillation to continue for as long as sixty minutes after the cessation of the infusion.

TABLE VII. RELATIONSHIP OF RATE OF ACETYLCHOLINE INFUSION TO AVERAGE VENTRICULAR RATE IN AURICULAR FIBRILLATION IN ONE DOG (NO. 9810)

ACETYLCHOLINE (DROPS PER MINUTE)	INFUSION (MG. PER MINUTE)	AVERAGE VENTRICULAR RATE (PER MINUTE)
52	7.4	80
30	4.0	116
18	2.0	150
12	1.75	170
112	16.0	33

8. *Observations Regarding the Spontaneous Termination of Auricular Fibrillation.*—The longest period of auricular fibrillation produced by a single rapid injection of acetylcholine was nine and one-half minutes. Auricular fibrillation, when produced, proceeded in the following manner: There was an increase in the ventricular rate as the fibrillation continued, until the ventricular rate stabilized itself at a rate of the order of 300 per minute. Spontaneous reversion to sinus rhythm was preceded by a pause which was always longer than the preceding cycle length. This pause was followed by the appearance of a regular ventricular rate, each QRS complex being preceded by a P wave. On several occasions we observed a transition from auricular fibrillation to auricular flutter, both pure and impure. On one occasion, following a single injection of 1.0 mg. of acetylcholine, auricular fibrillation ensued, with progression into pure flutter, which lasted for forty-three minutes and finally reverted to sinus rhythm. Reappearance of sinus rhythm is frequently preceded by slowing and increased amplitude of the *f* waves (coarse auricular fibrillation).

9. *Electrocardiographic Changes.*—In addition to the electrocardiographic changes which have been described, we have also observed the development of A-V dissociation, premature systoles of auricular and ventricular origin, nodal rhythm, and ventricular tachycardia. Changes in the electrocardiographic contour which we observed have been described in detail by others.[2,4,5]

10. *Side Effects of Acetylcholine Administration.*—Acetylcholine was found, in our experiments, to cause marked salivation, with the production of a thick, tenacious sputum which may interfere with respiration. There was stimulation of respiration and speeding of the cardiac rate after the initial slowing. With large doses, transitory convulsions, lasting for less than thirty seconds, may occur. Observations of similar effects have been made in man when large doses of acetylcholine have been used in shock therapy.[6] Other effects are described elsewhere.[17,18]

DISCUSSION

It is believed by many that the factors involved in the genesis of auricular fibrillation consist of (a) vagal hyperactivity and (b) a factor described by Nahum and Hoff as the "E" factor or excitatory factor.[12] These observers have included under the "E" factor such influences as thyroxin, electric shock, auricular distention, and mechanical stimulation of the auricles. Smith and Wilson[10] demonstrated that perfusion of the coronary arteries of the heart-lung preparation with anoxemic blood and Mecholyl often resulted in the occurrence of spontaneous auricular fibrillation even in the absence of auricular distention, and that such auricular fibrillation could be abolished by perfusion with oxygenated blood. They also demonstrated, in dogs, that asphyxia potentiated the action of Mecholyl in causing cardiac arrest and auricular fibrillation. Resnick[11] reported that anoxemia predisposed the faradically stimulated auricles to fibrillation even when vagal tone was completely removed, and that this predisposition occurred only early in the anoxemic period. The late effects of anoxemia produced by low oxygen mixtures appeared to inhibit the development of auricular fibrillation. A moderate degree of anoxemia produced a relative decrease in the refractory period of the auricular muscle and slowed conduction, both of which tend to favor the maintenance of auricular fibrillation. In Resnick's experiments performed on the dog's heart in situ, none of the animals developed auricular fibrillation spontaneously with anoxic anoxia, and faradic stimulation was used to initiate the auricular fibrillation.

In animals, vagal stimulation alone rarely leads to auricular fibrillation.[12] However, if the auricles are stimulated faradically during vagal excitation, auricular fibrillation nearly always occurs.[13] Lewis, Drury, and Bulger,[14] and also Andrus and Carter,[15] observed that vagal stimulation shortens the refractory period of auricular muscle remarkably, and that impulses falling early in the relative refractory phase may initiate auricular fibrillation. Andrus and Carter suggested that this is due to the setting up of re-entrant rhythms in muscle which is excitable but in which the conductivity has not yet returned to normal. It has been shown[14] that conductivity in the wall of the right auricle is practically unaffected by the vagus. When, however, the auricles are responding to stimuli

at rates above 300 per minute, then transmission of impulses through the auricles is facilitated by vagal stimulation by virtue of the shortening of the refractory period. In the over-all sense, the action of the vagus on the refractory period favors the development and maintenance of auricular fibrillation.

Numerous investigators have been able to produce auricular fibrillation in the dog and in man by using the parasympathomimetic agents, Mecholyl and acetylcholine. Goldenberg and Rothberger[4] noted that cats and dogs fibrillated far more readily following the administration of acetylcholine than following vagal stimulation. Iglauer, Davis, and Altschule[3] reported that Mecholyl given intravenously caused auricular fibrillation in seven of ten dogs tested. Several investigators have reported that the intra-arterial and intravenous injection of acetylcholine resulted in the production of auricular fibrillation, in isolated cases, in man. Of seventeen patients who received 40 mg. of acetylcholine injected into the common carotid artery, three developed transient auricular fibrillation.[7] Observations on thirteen patients who received 80 mg. of acetylcholine intravenously indicated the production of auricular fibrillation in one case only. Four additional patients received acetylcholine intravenously in doses of from 100 to 700 mg., with auricular fibrillation resulting in one patient.[6] No information regarding the hemoglobin levels in these subjects was given. Thus, it is clear that vagus-like substances alone may occasionally cause the development of auricular fibrillation in man and, more frequently, in dogs. In susceptible dogs we were able by continued infusion of acetylcholine to maintain auricular fibrillation for long periods. While the importance of vagal stimulation and anoxic anoxia upon the production of auricular fibrillation is apparent from the foregoing evidence, there are, so far as we know, no published data regarding the influence of anemia upon this arrhythmia. In this laboratory, Schlichter and associates,[19] using acetylcholine intravenously in the determination of circulation time in human subjects, have recently observed the production of auricular fibrillation in an occasional patient. In a subsequent analysis, Schlichter[1] found this was prone to occur in patients who were markedly anemic. Furthermore, following transfusion with whole blood, and with no other treatment, the auricular fibrillation was converted to sinus rhythm. This was taken to indicate that anemia may play a role in the genesis and maintenance of auricular fibrillation.

In our experiments, anemia, produced by each of the three different methods employed, resulted in an increased sensitivity of the heart toward the production of A-V block and auricular fibrillation by means of acetylcholine. Since it has already been shown that heightened vagal tone predisposes to auricular fibrillation, it may be reasoned that one of the ways in which anemia acts to favor the development of auricular fibrillation is through this mechanism.

We have, however, eliminated the vagal factor in testing the tendency to fibrillate by using a method of biological standardization in which we applied the same amount of vagal stimulation in the pre-anemic and anemic states. Under these conditions an increased tendency to fibrillate during anemia is still manifest, and must be due to other factors, including probably anoxia of the heart. We recognize that our method of assay depends upon the reaction of the A-V node, and we cannot state with certainty that a parallel degree of sensitivity occurs in the auricular muscle.

Acetylphenylhydrazine and *n*-propyl disulfide are two agents of distinctly different chemical composition, both of which produce a hemolytic type of anemia. It would appear that the common factor involved in the increased sensitivity in all procedures was associated with the anemia itself and was not a specific action of either the acetylphenylhydrazine or the *n*-propyl disulfide. We call attention to the increase in sensitivity which occurs shortly after the administration of either of these substances and which precedes any marked fall in the hemoglobin level. It is clear, however, that maximum sensitivity does not become manifest until the low point of the anemia is reached. And this point is not reached until several days have elapsed following the last dose of the drug. The explanation for the early development of sensitivity is not clear, nor is the explanation for the difference in sensitivities observed after acetylphenylhydrazine as compared with *n*-propyl disulfide. The explanation for both these factors may depend on the exact mechanism by which these hemolytic agents attack red blood cells. For hemorrhagic anemia a different mechanism must be invoked. It is probable, however, that anemia, per se, plays the major role in the mechanism of the sensitivity phenomena, and acts by decreasing the amount of oxygen available to the myocardium. Ventricular standstill resulting from A-V block and the increased work of the heart in anemia both contribute toward anoxia of the myocardium. We cannot, however, rule out the possibility that the sensitivity phenomena may be the reflection of a reduced esterase content of the blood. The factor of increasing rapidity of the circulation in anemia would seem to have been ruled out. It is known that the circulation time of the dog determined by the acetylcholine method varies from four to nine seconds, and is quite inconstant even in the same dog at rest. Measurements of the heart rates and circulation times from our own records lead us to consider that the increase in rate and the decreased circulation time are not sufficient in themselves to account for the increased sensitivity seen. Furthermore, on a number of occasions blood was aspirated into a syringe containing the minimal standardizing dose and a good admixture produced. Injection was delayed three to five seconds and was followed by A-V block. This indicates a relatively slow rate of hydrolysis of acetylcholine in the dog.

Sabine[16] has pointed out that the dog normally has a higher esterase activity in the plasma than in whole blood. This is the opposite of the situation found in man. When hemorrhagic anemia was produced in the dog, and the hematocrit fell, a fall of the plasma esterase occurred, but the whole blood esterase fell only slightly. This was due to a marked increase in the esterase content of the red cells. Similar studies in anemic states in man indicated that there was a marked rise in the esterase content of the cells which could not be wholly correlated with the rise in reticulocytes and young cells in the circulating blood. It is probable, therefore, that in anemia produced in dogs by the method described, the whole blood esterase falls little or not at all. However, since we do not know whether in the dog the plasma esterase or the cell esterase is of prime importance in hydrolyzing injected acetylcholine, it is impossible to rule out entirely a fall in plasma esterase as a contributing factor in the increased sensitivity to acetylcholine seen in anemia. Blood pH changes may also play a role here.

Our results are parallel to those of Smith and Wilson,[10] who demonstrated that asphyxia sensitizes the heart to Mecholyl, and to those of others[8,9] who showed that anoxemia enhances vagal cardiac action. Our results support the concept that anemia may play a role in the genesis of supraventricular conduction disturbances, including auricular fibrillation.

Finally, tracings obtained during our experiments offer no support for the concept that auricular fibrillation arises either from the operation of a parasystolic focus, or as the result of multiple, rapidly beating, ectopic pacemakers in competition with each other. The evidence fosters instead the belief that auricular fibrillation originates from a single initial impulse which undergoes re-entry within the auricles and gives rise to multiple continous re-entries from several points.

SUMMARY

1. The minimal dose of acetylcholine required to produce second degree A-V block (the minimal standardizing dose) was determined in thirty-one dogs. Although the minimal standardizing dose varies widely from animal to animal, it remains relatively constant for the same animal over long periods of time. The minimal standardizing dose bears a crude relationship to the hemoglobin level. Doses ten times and twenty times the minimal standardizing dose were also given. With such doses auricular fibrillation occurred in approximately 50 per cent of the animals tested.

2. Anemia was produced by phenylhydrazine, *n*-propyl disulfide, and hemorrhage. An increased sensitivity toward the development of A-V block and auricular fibrillation which roughly paralleled the course of the anemia was observed. Fifty per cent of the dogs which did not fibrillate with control injections of acetylcholine fibrillated following the onset of the anemia. Animals which fibrillated with control injections fibrillated during anemia with smaller doses of acetylcholine.

3. It is suggested that the increased sensitivity of the heart to acetylcholine in anemia is due to anoxia of the myocardium. Decreased concentration of effectiveness of cholinesterase may also play a role.

4. In dogs in which acetylcholine causes auricular fibrillation, there is a semidirect relationship between the dosage of acetylcholine given and the length of time during which the auricles fibrillate. There is also a relationship between the magnitude of the dose and the length of time during which the A-V block persists.

5. The development of auricular fibrillation was preceded in almost every instance by the occurrence of intra-auricular block and A-V block. It is suggested on the basis of the contour of our records and in support of previous reports from this department that auricular re-entry is the mechanism of the genesis of auricular fibrillation.

6. Electrocardiographic changes seen after the administration of acetylcholine included changes in the contour of the P waves and the T waves and shifts in the P-Q and S-T segments. Arrhythmias seen included auricular fibrillation and flutter, ventricular tachycardia, auricular and ventricular premature systoles, nodal rhythm, and A-V dissociation.

We are indebted to Dr. L. N. Katz for his suggestions and advice in the conduct of these studies and in the preparation of this report.

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THE INFLUENCE OF VAGAL ACTIVITY ON HEART BLOCK

A Study of the Effect of Oxygen, Mecholyl, and Atropine on Auriculoventricular Conduction Time

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THE reports of Bruenn,[1] Keith,[2] and Robinson[3] have shown clearly that large doses of atropine will shorten the P-R interval in a majority of the cases of partial heart block associated with acute rheumatic fever, as well as in certain vagotonic individuals. The findings of Logue and Hanson[4,5] indicated that this effect is not specific for acute rheumatic fever. The last named authors studied thirty-eight individuals with prolonged P-R intervals associated with various diagnoses and found that twenty-five (65 per cent) showed a return of the P-R interval to normal after administration of 0.96 mg. of atropine sulfate intravenously. There was no correlation between the clinical diagnosis and the effectiveness of atropine; however, it is of interest that in this group seven patients with rheumatic fever showed a return of the P-R interval to normal while six did not.

The reduction of the P-R interval in a control group was found by Bruenn[1] and Keith[2] to be less than that in rheumatic subjects with prolonged P-R intervals. This is due very probably to the fact that in normal individuals the P-R interval is closer to the minimum possible conduction time; hence, less shortening is possible. Bruenn[1] has interpreted these results to indicate that an increased vagal tone exists in acute rheumatic fever and has suggested that the site of the lesion may be in the central nervous system, probably in the medulla. Robinson[3] concurred in the opinion that an increased vagal tone exists in acute rheumatic fever with partial heart block. However, Logue and Hanson[4] felt that the effect of atropine did not preclude a pathologic change either in the heart muscle or in the conduction system and that the change in vagal tone might be due to altered physiology at the myoneural junction.

Dameshek, Loman, and Myerson[6] found that the P-R interval increased in almost every instance in normal individuals following the administration of Mecholyl. The maximum effect occurred within two to four minutes and the average percentage increase was 46 per cent. This was abolished within thirty to sixty seconds after the intravenous injection of atropine.

That heart block of all grades, including complete heart block, may be produced by asphyxia and succeeded by recovery, independent of vagus activity, was shown experimentally by Lewis and Mathison.[7] Persistent heart block of a high grade is generally considered to be due to intrinsic heart disease

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and temporary or transient block to be of vagal origin.[7,8] When heart block responds to atropine, the question arises as to whether the reduction in conduction time is due to the abolition of an increased primary central neurogenic effect or to a normal neurogenic effect upon a heart rendered more susceptible to vagal influence by some metabolic alteration in the conduction system, at the myoneural junction, or in the myocardium.

The present study was undertaken to investigate the effect of vagal activity on unselected cases of heart block. In addition to the effect of atropine, the effects of breathing 100 per cent oxygen and of the subcutaneous injection of acetyl-beta-methylcholine chloride (Mecholyl) on patients with heart block were studied.

METHOD OF STUDY

The subjects used in this study were fifty-one unselected patients from the wards and outpatient clinics of Duke Hospital whose electrocardiograms revealed a P-R interval of 0.21 second or over manifested in all leads, or higher degrees of heart block. No attempt was made to select the patients with regard to age, general condition, or diagnosis. The distribution of the patients according to age is shown in Table I, and the associated diagnoses are listed in Table II. Mecholyl was not administered to patients with a history of asthma or pulmonary disease.

TABLE I. AGE DISTRIBUTION OF PATIENTS

AGE (YEARS)	PATIENTS RECEIVING ATROPINE ALONE	PATIENTS RECEIVING OXYGEN, ATROPINE, AND MECHOLYL	TOTAL NUMBER OF PATIENTS IN SERIES
0– 9	1	0	1
10–19	1	4	5
20–29	3	6	9
30–39	4	2	6
40–49	4	4	8
50–59	5	3	8
60–69	7	3	10
70–79	2	0	2
80–89	2	0	2
Total	29	22	51

TABLE II. CARDIOVASCULAR DIAGNOSES OF PATIENTS COMPOSING GROUPS 1 AND 2

TYPE OF HEART DISEASE	PATIENTS RECEIVING ATROPINE ALONE	PATIENTS RECEIVING OXYGEN, ATROPINE, AND MECHOLYL	TOTAL
None demonstrable	6	5	11
Hypertensive	11	7	18
Arteriosclerotic	6	1	7
Rheumatic, active	2	5	7
Rheumatic, inactive	4	2	6
Congenital	0	1	1
Undiagnosed	0	1	1
Total	29	22	51

The patients were divided into two groups. In Group 1 there were twenty-one patients with partial heart block without dropped beats, four patients with partial heart block and dropped beats, and four patients with complete heart block. In Group 2 there were sixteen patients with partial heart block without dropped beats, four with partial heart block with dropped beats, and two with complete heart block. There were eight patients in each group who were receiving digitalis at the time of this study and of these only one was considered to be definitely intoxicated with the drug. Those patients with partial heart block with dropped beats and those with complete heart block are referred to in Tables IV and V.

In Group 1 a control electrocardiogram was taken and 2.0 to 3.0 mg. of sterile atropine sulfate solution were injected intravenously. (One child, 6 years of age, was given 0.8 milligram.) Electrocardiograms were repeated at various intervals. However, since the maximum effect occurred generally at twenty minutes, records taken at this interval were selected for comparison with the control.

In Group 2 a control electrocardiogram was taken, and the patient was allowed to breathe pure oxygen through a standard Benedict-Roth basal metabolism machine for five minutes. The electrocardiogram was repeated while the patient was still breathing pure oxygen. The oxygen was discontinued, and the needle of a syringe containing 2.0 mg. of sterile atropine sulfate solution was inserted into an arm vein and fixed in place by adhesive tape. The patient then was given a subcutaneous injection of 20 to 25 mg. of Mecholyl, and the electrocardiogram was repeated after an interval of three minutes. As soon as the electrocardiogram was completed, the atropine solution was injected and the final record was taken twenty minutes later.

When the P-R interval varied in any single record, the variation is shown in the table, and the mean is used for comparative purposes. The control record was used for comparison with those records taken after administration of the various drugs. Although it is realized that a P-R interval of 0.21 or even 0.22 second may be normal for some individuals, we have included these instances in this study under the diagnosis of no demonstrable heart disease when such delay was the only manifest abnormality present.

RESULTS

The results in the patients of Group 1 who showed partial heart block without dropped beats are summarized in Table III. Following the injection of atropine, the mean shortening of the P-R interval was 0.044 second, with a range 0.00 to 0.11 second. The mean increase in the cardiac rate was 28.1 beats per minute, with a range of -4 to $+82$ beats per minute. There was no strict correlation between the increase in rate and the shortening of the P-R interval. In one of the patients in this group blocked premature auricular beats appeared as the auricular rate increased. Among these patients with partial heart block without dropped beats, 52.4 per cent showed a return of the P-R interval to normal; 38.1 per cent showed a reduction of the P-R interval; and 9.5 per cent showed no change.

TABLE III. THE EFFECT OF ATROPINE ON HEART RATE AND DURATION OF P-R INTERVAL IN PATIENTS WITH PARTIAL HEART BLOCK WITHOUT DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE OR ASSOCIATED DIAGNOSIS	P-R INTERVAL BEFORE ATROPINE (SEC.)	VENTRICULAR RATE BEFORE ATROPINE	P-R INTERVAL AFTER ATROPINE (SEC.)	VENTRICULAR RATE AFTER ATROPINE	SHORTENING OF P-R INTERVAL (SEC.)	CHANGE IN VENTRICULAR RATE	DIGITALIS
1	Rheumatic, inactive	0.28	63	0.20	145	0.08	+82	No
2	Rheumatic, inactive	0.28	70	0.28	95	0.00	+25	Yes
3	Rheumatic, inactive	0.28	80	0.24	92	0.04	+12	No
4	Arteriosclerotic	0.24	42	0.20	80	0.04	+38	No
5	Hypertensive	0.22	83	0.20	103	0.02	+21	No
6	Dystrophia myotonica	0.23	68	0.21	79	0.02	+11	No
7	Dystrophia myotonica	0.23	62	0.23	58	0.00	− 4	No
8	Rheumatic, active	0.24	76	0.22	93	0.02	+17	No
9	Hypertensive and cystic lung disease	0.24	64	0.18	78	0.06	+14	Yes
10	Hypertensive	0.32	62	0.24	84	0.08	+22	No
11	None demonstrable	0.24	62	0.22	138	0.02	+76	No
12	Hypertensive	0.24	78	0.20	102	0.04	+24	No
13	Hypertensive	0.28	75	0.22	100	0.06	+25	Yes
14	Peptic ulcer	0.22	72	0.18	90	0.04	+18	No
15	Arthritis	0.26	58	0.20	58	0.06	0	No
16	Arteriosclerotic	0.23	63	0.18	72	0.05	+ 9	No
17	Arteriosclerotic	0.24	70	0.16	80	0.08	+10	Yes
18	Hypertensive	0.27	74	0.24	72	0.03	− 2	Yes
19	Bronchiectasis	0.26–0.28	74	0.16	111	0.11	+37	No
20	Rheumatic, active	0.20–0.21	67	0.19	115	0.015	+48	No
21	Arteriosclerotic	0.28	72	0.14–0.28	90* 72	0.07	+18	Yes

*After atropine, dropped beats appeared after premature auricular beats. Auricular rate 90, ventricular rate 72.

The effects of atropine on four patients not included in the figures just cited are summarized in Table IV. Two of these four had partial heart block with dropped beats; after atropine, one patient with a 2:1 A-V ratio showed an increase in the cardiac rate without a change in the P-R interval and the other showed a decrease in the P-R interval and the number of dropped beats. In one patient with frequent areas of sinoauricular block and nodal escape, as well as partial heart block, the sinoauricular block was abolished by atropine without an effect on the P-R interval. In one patient with partial heart block and a shifting pacemaker, nodal rhythm was produced by atropine.

Atropine had no effect on the A-V conduction time in four cases of complete heart block in this group. The effect on the auricular and ventricular rates is shown in Table V.

The results in the patients comprising Group 2 who exhibited partial heart block without dropped beats are summarized in Table VI. The average change in the cardiac rate after oxygen was breathed for five minutes was less than one beat per minute, and there was no change in the P-R interval. Therefore, these results are omitted from the table.

The mean change in the P-R interval after the injection of 20 to 25 mg. of Mecholyl subcutaneously was a decrease of 0.032 second with a range of +0.03 second to −0.14 second. The mean increase in the auricular rate was 25.7 beats per minute with a range of −1 to +50 beats per minute, and the mean increase in the ventricular rate was 20.3 beats per minute with a range of −42 to +50 beats per minute. In two patients with active rheumatic fever, A-V dissociation was produced in one and a 2:1 heart block in the other. The P-R interval was slightly increased in a third patient with no demonstrable heart disease. In this group the P-R interval returned to normal after Mecholyl in 37.5 per cent of the patients; decreased, but not to normal, in 31.3 per cent; increased in 25.0 per cent; and was unchanged in 6.2 per cent.

The mean change in the P-R interval in the patients comprising Group 2 after the injection of 2.0 mg. of atropine sulfate, which was given intravenously shortly after Mecholyl had been administered, was a decrease of 0.061 second with a range of 0.00 to −0.13 second. The mean increase in cardiac rate was 25.3 beats per minute with a range of −2 to +52 beats per minute. In two patients in whom A-V dissociation and 2:1 block had occurred following the injection of Mecholyl, 1:1 rhythm was restored after atropine, and the P-R interval either returned to the previous control level or was shortened. Following the injection of atropine, the P-R interval returned to normal in 62.5 per cent of the patients; decreased, but not to normal, in 25 per cent; and was unchanged in 12.5 per cent.

Four patients with partial heart block and dropped beats were given oxygen, Mecholyl, and atropine, in that order. The results are given in Table VII. In no instance did Mecholyl abolish dropped beats. However, in two patients the dropped beats were abolished by atropine, and the P-R interval shortened to normal or just beyond normal limits.

TABLE IV. THE EFFECT OF ATROPINE ON HEART RATE AND DURATION OF THE P-R INTERVAL IN PATIENTS WITH PARTIAL HEART BLOCK WITH DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE	CONTROL			AFTER ATROPINE			CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN VENTRICULAR RATE	CHANGE IN AURICULAR RATE	DIGITALIS
		P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE				
1	Hypertensive	0.19	80	40	0.19	104	52	0.00	+12	+24	No
2	Arteriosclerotic	0.15-0.36	88	55	0.23	78	75	−0.025	+20	−10	No
3	Hypertensive	0.24	*	35	0.24	82	82	0.00	+47		No
4	Arteriosclerotic	0.20†	36	36	(R-P) 0.14	60	60		+24		Yes

*This patient showed sinoauricular block with nodal escape. Atropine abolished sinoauricular block.
†Shifting pacemaker changed to nodal rhythm by atropine.

TABLE V. THE EFFECT OF ATROPINE ON AURICULAR AND VENTRICULAR RATES OF PATIENTS WITH COMPLETE HEART BLOCK*

CASE NO.	TYPE OF HEART DISEASE	CONTROL		AFTER ATROPINE		CHANGE IN VENTRICULAR RATE	CHANGE IN AURICULAR RATE	DIGITALIS
		AURICULAR RATE	VENTRICULAR RATE	AURICULAR RATE	VENTRICULAR RATE			
1	Hypertensive	A.F.†	38	A.F.†	38	0	0	Yes
2	Hypertensive	118	42	126	42	0	+8	No
3	Hypertensive	75	45	100	55	+10	+25	No
4	Rheumatic	70	26	90	31	+5	+20	No

*There was no effect on A-V conduction.
†A. F. = auricular fibrillation.

TABLE VI. THE EFFECT OF MECHOLYL AND ATROPINE ON HEART RATE AND DURATION OF P-R INTERVALS IN PATIENTS WITH PARTIAL HEART BLOCK WITHOUT DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE OR ASSOCIATED DIAGNOSIS	CONTROL		AFTER MECHOLYL					AFTER ATROPINE				DIGITALIS
		P-R INTERVAL (SEC.)	VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN VENTRICULAR RATE	P-R INTERVAL (SEC.)	VENTRICULAR RATE	CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN VENTRICULAR RATE	
1	None demonstrable	0.22-0.20	74	0.20-0.19	120	120	−0.015	+50	0.20-0.19	102	−0.015	+28	No
2	Rheumatic, active	0.24	110	*	113	97		−13*	0.24	120	0	+10	Yes
3	Rheumatic, active	0.36	76	0.22	94	94	−0.14	+18	0.24	115	−0.12	+39	Yes
4	None demonstrable	0.24	64	0.26-0.28	92	92	+0.03	+28	0.24	90	0	+26	No
5	Hypertensive	0.23	90	0.22	140	140	−0.01	+50	0.20	142	−0.03	+52	No
6	Rheumatic, active	0.24	100	0.20	112	56	−0.04	+12	0.16	112	−0.08	+12	Yes
7	Arteriosclerotic	0.21-0.24	71	0.20-0.21	70	70	−0.02	−1	0.20	74	−0.025	+ 3	Yes
8	None demonstrable	0.33	66	0.24	112	112	−0.09	+46	0.20-0.22	95	−0.12	+29	No
9	Cardiac enlargement undiagnosed	0.28-0.32	88	0.28-0.32	100	100	0	+12	0.22-0.24	118	−0.07	+30	No
10	Myxedema	0.22	68	0.24	90	90	+0.02	+22	0.18	100	−0.04	+32	No
11	Rheumatic, active	0.28	92	0.24	108	108	−0.04	+16	0.16-0.18	143	−0.11	+51	Yes
12	Rheumatic, active	0.23	112	0.26	140	70	+0.03	−42†	0.22	110	−0.01	− 2	No
13	None demonstrable	0.29	92	0.20	140	140	−0.09	+48	0.19	128	−0.10	+37	No
14	Hypertensive	0.26-0.32	72	0.20	100	100	−0.09	+28	0.16	94	−0.13	+22	No
15	Hypertensive	0.21	60	0.18	86	86	−0.03	+26	0.12	84	−0.09	+24	Yes
16	Rheumatic, inactive with subacute bacterial endocarditis	0.23	110	0.20	136	136	−0.03	+26	0.17-0.19	122	−0.05	+12	No

*A-V dissociation appeared after Mecholyl; following atropine, sinus rhythm was restored.
†2:1 block appeared after Mecholyl; atropine restored sinus rhythm.

TABLE VII. THE EFFECT OF MECHOLYL AND ATROPINE ON HEART RATE AND DURATION OF P-R INTERVAL IN PATIENTS WITH PARTIAL HEART BLOCK WITH DROPPED BEATS

CASE NO.	TYPE OF HEART DISEASE	CONTROL			AFTER MECHOLYL						AFTER ATROPINE						DIGITALIS
		P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN AURICULAR RATE	CHANGE IN VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN AURICULAR RATE	CHANGE IN VENTRICULAR RATE	
1	Hypertensive	0.20-0.32	65	44	0.16-0.30	100	60	—0.03	35	15	0.20-0.21	90	90	—0.065	25	46	Yes
2	Hypertensive	0.20-0.24	90	89	0.20	72	70	—0.02	—18	—19	0.20	124	62	—0.02	34	—28	No
3	Hypertensive	0.18-0.26	80	40	0.20-0.28	80	78	+0.02	0	38	0.20	86	86	—0.02	6	46	Yes
4	Hypertensive	0.20	76	38	0.20	62	35	0	—14	— 3	0.20	106	53	0	30	15	No

TABLE VIII. EFFECT OF MECHOLYL AND ATROPINE ON HEART RATE AND DURATION OF P-R INTERVAL IN PATIENTS WITH COMPLETE HEART BLOCK

CASE NO.	TYPE OF HEART DISEASE	CONTROL			AFTER MECHOLYL						AFTER ATROPINE						DIGITALIS
		P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN AURICULAR RATE	CHANGE IN VENTRICULAR RATE	P-R INTERVAL (SEC.)	AURICULAR RATE	VENTRICULAR RATE	CHANGE IN P-R INTERVAL (SEC.)	CHANGE IN AURICULAR RATE	CHANGE IN VENTRICULAR RATE	
1	Congenital heart block	0.20	68	45	0.20	120	60	0	52	15	0.19	140	70	—0.01	72	25	No
2	Rheumatic, inactive		78	40		78	40		0	0		126	70		48	30	No

Oxygen, Mecholyl, and atropine, administered in that sequence, had no effect on one patient with complete heart block other than an increase in both auricular and ventricular rates after atropine. In a second patient with A-V dissociation, 2:1 block occurred after the administration of oxygen and remained after the administration of both Mecholyl and atropine. These results are shown in Table VIII.

There was no predictable relationship between the reaction to atropine or Mecholyl and the presence or absence of digitalis in either group. One patient in Group 2 who was thought to be intoxicated with digitalis (Case 3, Table VII) showed slight prolongation of the P-R interval with a decrease in the number of dropped beats after Mecholyl, and a 1:1 response with a normal P-R interval after atropine.

The blood pressure was recorded in about one-half of the patients in Group 2, and in general there was a drop after the injection of Mecholyl with an immediate rise after atropine followed by a gradual fall to the previous control level at the end of fifteen minutes.

No serious reactions were observed to follow the administration of any of these drugs under the conditions of these experiments. One patient complained of discomfort because of tachycardia following the injection of atropine and several noted dizziness or slight drowsiness. The majority of the patients who received Mecholyl noted temporary discomfort consisting of sweating, increased salivation, tightness in the chest, and dyspnea. In no case did the chest symptoms suggest coronary insufficiency, and in no case did the electrocardiogram show depression of the RS-T segment consistent with coronary insufficiency. In each instance the unpleasant symptoms from Mecholyl were abolished within sixty seconds by the intravenous injection of atropine. The effects of atropine generally were dissipated at the end of two hours.

DISCUSSION

In this study the mean shortening of the P-R interval after the administration of atropine to unselected patients with partial heart block was found to be of similar magnitude to that reported by Keith[2] and by Robinson,[3] who studied patients with rheumatic fever, but not so great as that reported by Bruenn.[1] Our results in general confirm the findings of Logue and Hanson[4] that atropine will shorten to normal, or significantly reduce the P-R interval in a majority of unselected cases of partial heart block, regardless of the etiology or the associated disease. An atropine test, therefore, is of little value in differentiating between heart block of neurogenic origin and that due to myocardial disease.

The effects of Mecholyl and atropine, when given in this sequence, upon the cardiac rate and the blood pressure were found to agree in general with those observed by Dameshek, Loman, and Myerson.[6] Following the administration of Mecholyl, if atropine is given intravenously at the time of the fall in blood pressure, there is a prompt, sharp, and sudden rise in blood pressure above the previous normal level. This suggests that when the action of

Mecholyl is abolished by atropine there is a reflex pressor response from an increase in circulating adrenalin as a result of the initial fall in blood pressure. In favor of this view is the fact that when atropine was given prior to Mecholyl to four normal subjects there was no significant fall in blood pressure initially and no secondary rise in blood pressure. The pressor response, therefore, is probably of the same nature as that occurring during the histamine test for pheochromocytoma suggested by Roth and Kvale[9] but differs very greatly in magnitude.

We found the change in the P-R interval which followed the injection of Mecholyl to be unpredictable, in contradistinction to the findings of Dameshek, Loman, and Myerson.[6] These authors, using normal individuals, noted an increase in A-V conduction time in almost every instance, while it was observed by us that in patients with partial heart block without dropped beats, well over one-half showed a decrease, and only one-fourth showed a definite increase in the P-R interval.

Acetylcholine in large dosage has been shown by Hoffmann and associates[10] and by McDowall[11] to produce a stimulating effect on the atropinized heart but not on the unatropinized heart in isolated perfusion experiments. While the results of heart-lung experiments cannot be applied directly to human pharmacology, they do suggest the complex nature of the problem. The paradoxical effects of Mecholyl on cardiac rate and A-V conduction time in the human subject indicate that the magnitude of the various side effects of the drug, unrelated to its direct action on the myoneural junction, often may be as great as the vagomimetic effect.

The unpredictable effect of Mecholyl on A-V conduction time in patients with partial heart block suggests that this drug is of no value in evaluating the part played by vagal activity in unselected cases of heart block. It is apparent from our observations that heart block, per se, does not contraindicate the use of Mecholyl.

These results do not preclude the possibility that the action of these drugs on A-V conduction time is related to changes in coronary blood flow. Although we produced no significant change by having the patients breathe pure oxygen, this does not eliminate the possibility that changes in the caliber of the vessels supplying the conducting tissues may be of importance. Wedd,[12] Essex and associates,[13] and Katz and Lindner[14] have shown that Mecholyl increases the coronary blood flow. The effects of atropine on coronary blood flow are somewhat conflicting. Essex and co-workers[13] found atropine to increase coronary blood flow, while Katz and Lindner[14] observed a weak vasoconstrictor effect on the coronary arteries. Halsey[15] noted that partial heart block associated with digitalis intoxication in the dog could be reduced significantly by amyl nitrite but believed this to be due to a lessened vagal effect as a result of a drop in blood pressure. It should be pointed out, however, that large doses of digitalis in the dog cause constriction of the coronary vessels. The results of our observations on the response of human subjects to atropine, Mecholyl, and oxygen do not serve to delineate the physiologic mechanisms involved in the production of heart block. These drugs do not determine whether

alterations of conduction time are due to increased central neurogenic effects or to normal neurogenic influences acting upon hearts rendered more susceptible to vagal influence as the result of metabolic changes in the conducting system, in the myoneural junction, or in the myocardium itself.

SUMMARY AND CONCLUSION

Fifty-one cases of heart block associated with various etiological factors were studied electrocardiographically for changes in the P-R interval after the administration of atropine. In twenty-two of these cases the effects of oxygen and Mecholyl were analyzed and the results compared.

Both atropine and Mecholyl were found to decrease the P-R interval in a majority of these cases, but atropine proved the more effective drug. It is concluded that atropine, Mecholyl, and oxygen are of no value in determining either the etiology of heart block or the underlying physiologic mechanisms in human subjects.

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RELATIONSHIP OF DICUMAROL ABSORPTION TO GASTRIC FREE HYDROCHLORIC ACID

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THE extreme variability of the prothrombin time response to similar dosages of Dicumarol is a well-established fact. This work was prompted by Dr. Irving Wright of New York City, who raised the question regarding a possible relationship between Dicumarol absorption and gastric acidity. This study, therefore, is concerned chiefly with the relationship of prothrombin response in individuals to the amount of free hydrochloric acid present in the gastric contents after a set dosage of Dicumarol has been given.

METHODS

The subjects studied were all postoperative patients, with the exception of one patient with thrombophlebitis. Most of the patients had had a combined abdominal-perineal resection for carcinoma of the rectum. The average age of the group was 60.5, ranging from 34 to 83 years of age.

The amount of free hydrochloric acid was determined by the histamine fractional test. The figures reported in the study represent the highest degree of free hydrochloric acid found in any one fractional specimen.

The prothrombin time was determined by the same method recommended by Quick[1] with one exception. We used 5.0 c.c. of whole blood to 1.0 c.c. of 1.4 per cent sodium oxalate when we collected the specimens. The results were then recorded as prothrombin concentration, which was determined by the curve shown in Fig. 1. The curve was made with Difco thromboplastin. The diluent used for the blood in making up the curve was saline. Most of the thromboplastin used was Difco. However, some of the early cases were recorded with rabbit-brain thromboplastin freshly made up in our laboratory. The blood for the prothrombin time determinations was drawn at approximately 11 A.M. daily.

A set dosage of Dicumarol was used. Each patient was given 300 mg. at 6 P.M. of the first day. They were then given 150 mg. at 6 P.M. on the second day. Two subjects were not given the 150 mg. on the second day because the prothrombin concentration was so low that this probably would have been dangerous.

In addition to these determinations, each patient had a bromsulfalein retention liver function test and a blood urea calculation.

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DATA

The patients studied were divided into three groups. The first group showed a true achlorhydria. The second group were those having at least one fractional specimen from 1° free hydrochloric acid through 70° free hydrochloric acid. The third group included those with more than 70° free hydrochloric acid.

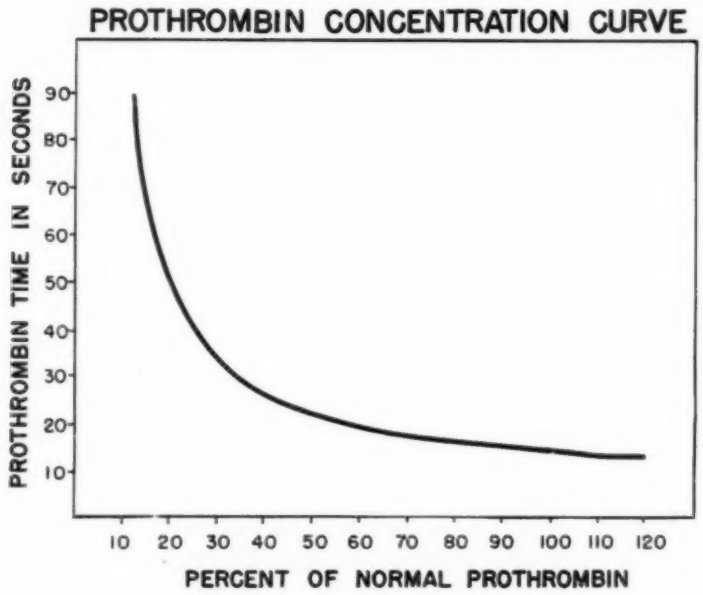

Fig. 1.

The prothrombin concentration average of each group was then calculated for the second, third, and fourth days and compared. The range of prothrombin concentration was also compared in the various groups. The following three tables show the data obtained (Tables I, II, and III).

TABLE I. PROTHROMBIN CONCENTRATION ONE DAY AFTER 300 MILLIGRAMS OF DICUMAROL

	ACHLORHYDRIA	0° THROUGH 70° FREE HCL	70° + HCL
Number of cases	5	10	17
Average prothrombin concentration (per cent)	66.2	62.4	60.5
Range of prothrombin concentration (per cent)	44–77	32–100	22–100

TABLE II. PROTHROMBIN CONCENTRATION THIRD DAY AFTER GIVING 300 MILLIGRAMS OF DICUMAROL THE FIRST DAY AND 150 MILLIGRAMS THE SECOND DAY

	ACHLORHYDRIA	0° THROUGH 70° FREE HCL	70°+ HCL
Number of cases	5	9	15
Average prothrombin concentration (per cent)	34.6	36.6	39.3
Range of prothrombin concentration (per cent)	30–38	21–54	22–68

TABLE III. PROTHROMBIN CONCENTRATION FOURTH DAY AFTER 300 MILLIGRAMS OF DICUMAROL THE FIRST DAY AND 150 MILLIGRAMS THE SECOND DAY

	ACHLORHYDRIA	0° THROUGH 70° FREE HCL	70°+ FREE HCL
Number of cases	4	8	15
Average prothrombin concentration	29.8	33.3	39.7
Range of prothrombin concentration	26–34	15–86	15–85

Similar data were then computed on two sets of patients. The first set, containing nineteen patients, had a bromsulfalein retention of 10 per cent or less. The second group contained ten patients having a bromsulfalein retention ranging from 16 per cent to 72 per cent, with an average of 32.8 per cent.

RESULTS

The one most consistent finding was that of an extreme degree of variability in the response of prothrombin time to Dicumarol.

There is a slight increase in the average prothrombin concentration going from the achlorhydria to the hyperacidity groups. However, all groups, especially the two groups containing free hydrochloric acid, showed such a marked variability of response to Dicumarol that the slight increase of the average prothrombin concentration would not seem to be significant.

A definite decrease in the range of variability was noted in the achlorhydria group. Likewise, the group showing free hydrochloric acid revealed a wider fluctuation of prothrombin concentration. However, further breakdown of this group did not reveal any direct relationship between the level of free hydrochloric acid and the prothrombin concentration.

It is the opinion of the writers that the data indicate that there is no correlation between increased or decreased absorption of Dicumarol and gastric acidity.

An interesting finding was the comparison of the prothrombin concentration response in relationship to the bromsulfalein retention liver function test. The differences, surprisingly, were not marked. The range of prothrombin concen-

tration varied from a strong response to very little response. On the first day and fourth day there was some evidence of increased prothrombin response in the group with increased bromsulfalein retention; however, on the third day the same group revealed a decreased prothrombin response, again demonstrating the variability.

CONCLUSIONS

1. A comparison has been made of the prothrombin response to Dicumarol with the amount of free hydrochloric acid present in the gastric contents and no relationship was found.

2. The extreme variability of the prothrombin time following Dicumarol administration was again demonstrated.

3. A decreased range of variability was noted in the achlorhydria group. The significance of this is not understood at the present time.

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Clinical Reports

DISSECTING ANEURYSM OF AORTA WITH HEMORRHAGIC INFARCTION OF THE SPINAL CORD AND COMPLETE PARAPLEGIA

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IT IS well known that the clinical picture of dissecting aneurysm of the aorta varies widely both as to symptomatology and objective findings. The neurological manifestations are often bizarre, but, if properly interpreted, may lead to a correct ante-mortem diagnosis.[29] Instances of paraplegia and paraparesis caused by spinal cord ischemia which results from rupture and thrombosis of the intercostal arteries have occurred, but the entity is rare, and in most of the reported cases, the spinal cord either has not been examined, or has been studied incompletely. In a survey of 698 recorded cases of dissecting aortic aneurysm, we found only three in which the spinal cord was shown to have been the seat of ischemic necrosis and hemorrhagic infarction.

This paper deals with the clinical and necropsy observations on such a case, which exhibited a feature not hitherto observed, namely, a spinal subarachnoid hemorrhage.

CASE REPORT

H. G. L., a 56-year-old Negro man, while addressing a group of fellow ministers on the afternoon of July 17, 1947, was stricken by a sudden sharp, nonradiating upper substernal pain. After a few seconds this pain disappeared, and following a moment's hesitation, he was able to continue speaking. Five minutes later he experienced a second similar pain in the lower substernal region which radiated into the epigastrium and caused him to collapse and fall to the floor. The pain did not radiate to the back, arms, neck, or jaw. He was carried down from the rostrum and in about thirty minutes he lost consciousness and remained so for an hour. He was removed to the emergency ward of a local hospital, where a diagnosis of acute gastroenteritis was made. After administration of sodium luminal he was observed for several hours, and discharged. During this period of time he had recurrent attacks of generalized, burning, abdominal pain, each lasting five to ten minutes, with complete relief between attacks. At first the pain radiated bilaterally to the back, but later radiation was confined to both flanks.

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On the morning of July 18 the episodes of abdominal pain became more severe and more frequent. He became nauseated and vomited a clear fluid. At 9 A.M. he arose from bed and observed that the right foot was partially paralyzed, one hour later the entire right leg was completely paralyzed, and by noon he had complete paraplegia with numbness from the waist down. At 8 P.M. on July 19, approximately fifty-four hours after the onset of the initial attack of substernal pain, he was admitted to the Cleveland City Hospital with complete motor and sensory paralysis from the waist down. Intermittent abdominal pain radiating to both flanks continued for two days thereafter.

The past history threw no light on his present disability. He had been a minister for seventeen years, was married, and had two healthy children. He had enjoyed good health and had no knowledge of syphilis, tuberculosis, or cardiovascular disease.

Physical examination revealed a well-developed, well-nourished 56-year-old Negro man, complaining of intermittent abdominal pain in spite of heavy sedation with morphine. The temperature was 38° C., the respiratory rate 18, the pulse rate 100, and the blood pressure 150/90 in both arms. The blood pressure did not vary significantly throughout his hospital course. The skin was cool and dry above the umbilicus, warm and moist below. The pupils were equal and reacted well to light and in accommodation. The ocular fundi showed moderate sclerosis of the arteries and the discs were well outlined. The pharynx was diffusely and slightly hyperemic; the trachea was in the midline and no tug was noted. There was moderate nuchal rigidity. The thorax was symmetrical and expansion was bilaterally equal and unrestricted. Percussion and auscultation of the lungs revealed nothing abnormal. The heart was moderately enlarged to the left by percussion. The cardiac mechanism was normal except for numerous premature beats. The heart sounds were not unusual; the aortic second sound was accentuated; and a Grade 2 systolic murmur was heard at the apex. All accessible peripheral arteries were moderately thickened and tortuous. All accessible pulses on the two sides were equal and full. The abdomen was slightly distended but not tender to deep palpation. The liver, kidneys, and spleen were not felt, but the urinary bladder dullness was percussed several finger breadths above the pubic symphysis. Rectal examination revealed poor sphincter tone.

A neurological examination disclosed paralysis of both legs and complete loss of sensation from the level of the eighth dorsal segment down, with a band of hyperesthesia above this level corresponding to the distribution of the seventh dorsal segment. The abdominal and cremasteric, as well as the lower deep tendon reflexes, were totally absent. Ankle and patellar clonus and Babinski's sign were not present. Kernig's sign was absent. The upper reflexes were equal and active.

Laboratory work revealed the urine to be clear amber, acid, with a specific gravity of 1.025 plus 4 albumin, and 1.5 per cent sugar. An occasional white blood cell was present. On subsequent repeated examinations the albumin and sugar disappeared, although occasional white cells were constantly present. The hemogram showed 16 Gm. of hemoglobin, 4,700,000 red blood cells, and 19,600 white cells with a moderate shift to the left. White counts repeated on the sixth and seventh hospital days were 14,000 and 12,200, respectively. The electrocardiogram showed left axis deviation.

Because of the history, course, and findings, a tentative diagnosis was made of dissecting aneurysm of the aorta with paraplegia due to rupture of intercostal arteries and ischemia of the spinal cord. The patient was placed on complete bed rest and given large doses of morphine. These measures, however, failed to control his pain completely. An indwelling catheter was left in the bladder after removal of 1,300 c.c. of urine. The blood Wassermann reaction was negative. The blood urea nitrogen on admission was 50.4 mg. per cent, and dropped to 20.3 mg. per cent four days later. An admission chest film on July 20 showed the heart to be enlarged, the transverse diameter measuring 174 millimeters. A diffuse aneurysmal dilatation of the aorta with slight displacement of the trachea to the right was noted (Fig. 1).

On July 20, his second hospital day, a lumbar puncture was done, the needle being introduced between the fourth and fifth lumbar vertebrae. The spinal fluid pressure was 140 mm. H_2O, which dropped to zero after removal of a few cubic centimeters. Following centrifugation, the supernatant fluid was xanthochromic. A cisternal puncture was done on July 21, and again a grossly bloody spinal fluid was withdrawn, under a pressure of 330 mm. of water. A rise in pres-

sure was demonstrated by jugular compression, but strong abdominal pressure raised the level only 5 millimeters. A lumbar puncture repeated on July 22 revealed the same findings, with a negative Queckenstedt and reversed negative Queckenstedt. The spinal fluid Wassermann reaction was negative.

Because of the subarachnoid hemorrhage and evidence of complete block, the working diagnosis was changed to hematomyelia due either to thrombosis of the anterior spinal artery with hemorrhage, or bleeding from a tumor, possibly a hemangioma. It was felt that the subarachnoid block might be due to a cord tumor, and further diagnostic work was done. A posterior-anterior film of the chest on July 23 showed no change. X-ray films of the spine, including several cone-down views, failed to reveal any abnormality. A neurological consultation was held on July 22, and no change in the objective findings was noted other than an extension of the area of hyperesthesia on the trunk to the level of the fifth dorsal segment. The patient was incontinent of feces

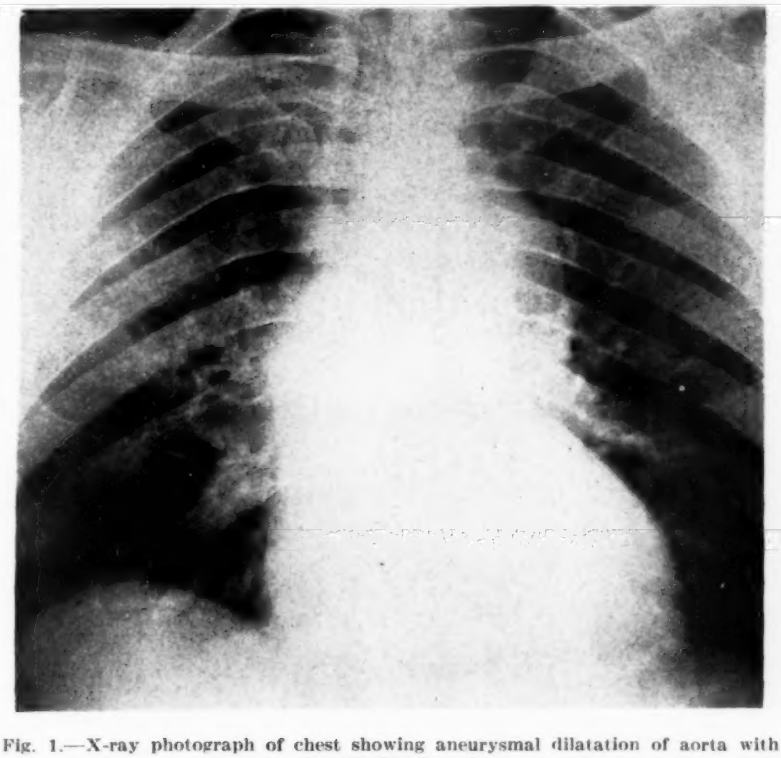

Fig. 1.—X-ray photograph of chest showing aneurysmal dilatation of aorta with trachea displaced to right.

and still required constant urinary drainage. The neurologists confirmed the presence of a complete cord transection producing the picture of spinal shock, and recommended that myelograms be done. The latter were performed on July 25, and were considered nondiagnostic.

On July 24 the patient was seen by a consultant in neurosurgery, who likewise suggested the possibility of a vascular tumor, probably at the level of the seventh dorsal segment, with rupture and subarachnoid hemorrhage. An operation was advised, but immediately following the induction of gas-oxygen-ether anesthesia, the patient expired on the table before an incision could be made. Death occurred on July 26, nine days after the onset of symptoms.

Autopsy.—Anatomical Diagnosis: Dissecting aneurysm of the aorta. Hemorrhagic infarct of spinal cord. Subarachnoid hemorrhage of spinal cord and brain. Arteriolar nephrosclerosis, slight. Cardiac hypertrophy and dilatation (450 grams). Arterial sclerosis (aorta, iliac, cerebral, and visceral, moderate; coronary, slight).

Gross Pathology (Dr. H. Goldman): "The heart is enlarged and weighs 450 grams. Three centimeters above the aortic ring there is a straight clean tear of the intima and part of the media, with finely serrated edges, extending completely around the aorta. The dissection extends proximally to the base of the aortic valve, and distally into the common iliacs just beyond the bifurcation. The dissection of the aortic wall involves nearly its entire circumference throughout its entire length, and extends likewise into the first centimeter of the innominate, left subclavian, left common carotid, right subclavian (which arises anomolously directly from the arch, one centimeter distal to the origin of the left subclavian), coeliac, and superior mesenteric arteries. Re-entry is noted in the left subclavian. The renal arteries are dissected to the hilus but are fully patent. The vertebral arteries are patent and not involved, although the lumen of the left is slightly narrowed at its origin by an arteriosclerotic plaque. All the intercostal and lumbar

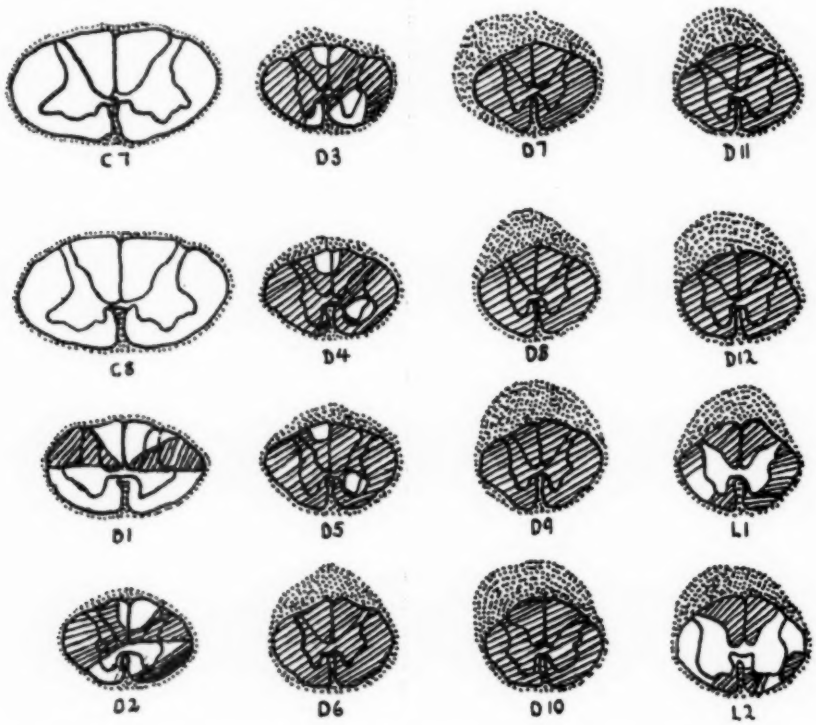

Fig. 2.—Spinal cord involvement from level of *C7* to *L2*. Stripes indicate areas of necrosis, hemorrhage, demyelinization, and inflammatory infiltration. Stippled areas represent subarachnoid clot which in some sections showed early organization.

arteries are completely shorn from the aorta, many of them showing thrombus formation. The intimal surface of the aorta is the seat of only moderate arteriosclerosis, proximal to the superior mesenteric artery.

"The pericardial sac is tense and contains 75 c.c. of thin bloody fluid. The pericardial surface is granular and contains adherent fibrin tags. Between the aorta and pulmonary conus in the pericardial reflection there is a friable clot, but an area of rupture into the pericardial space cannot be demonstrated.

"The brain is grossly normal, but there is a layer of blood in the subarachnoid space, involving predominantly the posterior aspect of the cerebral hemispheres, the cerebellum, and the base of the brain posteriorly.

"The cord is removed in toto. On opening the dura, a subarachnoid hemorrhage with clot formation is present over its entire length and circumference. This is most marked from the first thoracic to the first lumbar segments, and reaches its maximum from the seventh dorsal to the twelfth dorsal segments. The cord is soft and diffusely swollen, this being most marked in the same regions where the clot is most extensive. Examination after fixation reveals adherent clot most prominent on the dorsal surface, as described, with a maximum thickness of 3.0 mm. Cut sections of the cord were examined from the level of the seventh cervical to the second lumbar segments, and nowhere can the usual divisions of the cord into white and gray matter be seen."

Microscopic Pathology (Dr. W. Morningstar): "Sections of the aorta in the region of the tear show diffuse cystic necrosis of the media. There is no intimal change in the immediate neighborhood of the tear. Serial sections of the spinal cord from the seventh cervical to the second lumbar segments are examined following staining with hematoxylin and eosin and Weigert's myelin stain. The seventh and eighth cervical segments are uninvolved. The first dorsal segment shows predominantly demyelinization and myelomalacia with minimal hemorrhage just posterior to the central canal. This increases in extent until the level of the sixth dorsal segment, where the involvement is complete, resulting in diffuse hemorrhage and necrosis. At the twelfth dorsal segment the change is one of complete necrosis and marked hemorrhage. The first lumbar segment shows necrosis and patchy hemorrhage with the gray matter essentially spared, and the second lumbar segment shows degeneration confined mainly to the posterior columns with an acute inflammatory infiltration of polymorphonuclear leucocytes. For a diagrammatic representation of the changes found at various levels of the spinal cord see Fig. 2.

"The subarachnoid clot shows early organization from the fifth dorsal to the second lumbar segment. Although in one area a small break is demonstrated in the anterior spinal artery, we cannot be certain that this affords adequate explanation of the subarachnoid hemorrhage. No source is found in the brain, and it is felt that the subarachnoid hemorrhage present here is due to extension from below upwards."

DISCUSSION

Neurological complications of dissecting aneurysm of the aorta are by no means uncommon. The actual incidence, however, is difficult to determine, and varies in different series. The reasons for this would appear to be several. As many as 35 per cent of such patients die within the first hour before they have been seen by a physician or before they develop localizing signs.[21] In addition, the nature of the illness is such as to turn the examiner's attention away from the neurological manifestations unless they are quite apparent. Finally, it becomes obvious in reviewing the literature that complete clinical and pathological descriptions are often lacking, usually because of the author's interest in one particular phase of the disease. Thus, in reviewing 698 recorded cases, we found only 424 that were in any way suitable for analysis. Definite neurological complications were found in eighty-nine cases, or 21 per cent, as compared with 11 per cent in Shennan's[23] series, 18 per cent in the series of Baer and Goldburgh,[1] and 29 per cent in the cases collected by Weisman and Adams[29] (Table I). Following the scheme proposed by the last-named authors, forty-one patients with neurological manifestations had ischemic neuropathy, twenty-six had ischemia of the brain, and twenty-two had ischemia of the spinal cord. In some instances, more than one of these features was combined. If doubtful cases were included, which we discarded because of insufficient authenticity or incomplete clinicopathological correlation, our percentage would approximate the incidence reported by Weisman and Adams.[29]

TABLE I. INCIDENCE OF NEUROLOGICAL MANIFESTATIONS IN COLLECTED CASES OF DISSECTING ANEURYSM

AUTHOR	CASES ANALYZED	NEUROLOGICAL COMPLICATIONS	
		NO.	%
Shennan[23]	316	45	11
Weisman and Adams[29]	38	11	29
Baer and Goldburgh[1]	44	8	18
Present Series	424	83	21

We found a total of twenty-eight well-authenticated instances of paraplegia and paraparesis, an incidence of 6.6 per cent (Table II). Of these, ten represented ischemia of the spinal cord, eleven ischemic neuropathy, three a combination of these two factors, and four could not be determined (Table III). The disparity between the number of patients showing signs of spinal cord ischemia and those resulting in paraplegia lies in the fact that there is probably some gross quantitative relationship between the number of intercostal and lumbar segmental arteries interrupted and the degree of disability resulting. While it is true that disruption of all or most of these vessels results in paralysis, this does not always obtain, since instances have been reported in which no cord signs were noted in spite of marked loss of blood supply as shown later by autopsy.[9,12,37] The cause of radiation of pain to the lower legs has been a subject of some dispute, being attributed by some to stimulation of nerve endings along the course of dissected vessels,[17,31] and by others to the initial transient spinal cord ischemia as the dissection extends downward.[9,26] Reichert and associates[18] have called attention to claudication of the thighs resulting from arteriosclerosis of the lumbar segmental arteries, which, along with cramping of the calves, is a not uncommon occurrence with intercostal artery separation of extensive degree.

Coleman,[6] in 1898, reported the first case of paraplegia due to spinal cord ischemia, but in only three instances has there been unequivocal evidence, demonstrated by pathological study, of injury to the cord consisting of ischemic necrosis and hemorrhagic infarction: those of Kalischer (1914), Reitter (1916), and Weisman and Adams (1944). Rogers,[21] in 1939, and Tuohy and his co-workers,[26] in 1941, for the first time in the American literature, called specific attention to spinal cord ischemia, but unfortunately little mention was made of post-mortem findings in the spinal cord.

The differential diagnosis of localized spinal cord lesions resulting in bilateral manifestations has been discussed in previous papers, and quite thoroughly in regard to dissecting aneurysm by Weisman and Adams,[29] but the presence of a bloody spinal fluid and subarachnoid block in our case deserves some comment. This is of interest, since a clear spinal fluid on puncture has been considered a differential diagnostic criterion favoring the diagnosis of dissecting aneurysm.[21] Except for a bloody spinal fluid, our case is quite similar to those of Weisman and Adams[29] and of Reitter.[19] The latter commented at length on the absence of subarachnoid hemorrhage in his case, and suggested that the spinal fluid pressure

TABLE II. TWENTY-EIGHT CASES OF PARAPLEGIA AND PARAPARESIS RESULTING FROM DISSECTING AORTIC ANEURYSM (698 CASES WERE REVIEWED AND 424 WERE ANALYZED)

AUTHOR	YEAR	TYPE OF INVOLVEMENT	PATHOLOGICAL ANATOMY
Swaine and Latham[24]	1855–6	Paraplegia, transient	Common iliac obstruction
Sainet[22]	1857	Paraplegia, permanent	Unknown
Lebert[5]	1857	Paraplegia, permanent	Unknown
Dickenson[7]	1862	Paraplegia, permanent	Combined: obstruction of aorta by intimal bulge beyond origin of left subclavian artery
Gordon[11]	1863–4	Paraplegia, permanent	Common iliac obstruction
Barth[3]	1871	Paraplegia, permanent	Unknown
Coleman[6]	1898	Paraplegia, transient	Spinal cord ischemia
Ka'ischer[13]	1914	Paraplegia, permanent	Infarction of spinal cord
Reitter[19]	1916	Paraplegia, permanent	Infarction of spinal cord
Bard and Gardere[2]	1925	Paraplegia, permanent	Probable compression of lumen of aorta by intimal bulge
Tyson[27]	1931	Paraplegia, permanent	Spinal cord ischemia
Lawrence[14]	1935	Paraplegia, permanent	Compression of iliac lumens by dissection
Glendy, Castleman and White[10]	1937	Paraparesis, permanent	Lower aortic thrombosis
Rogers[21]	1939	Paraplegia, permanent, right, transient, left	Combined: spinal cord ischemia and iliac obstruction
Cabot Case No. 25382[4]	1939	Paraplegia, permanent	Common iliac obstruction by intimal bulge
East[8]	1939	Paraplegias, transient (two episodes 3.5 years apart)	Common iliac obstruction
Lowell[16]	1940	Paraplegia, duration unknown	Unknown
Tuohy and associates[26]	1941	Paraplegia, permanent	Common iliac obstruction by intimal bulge
Tuohy and associates[26]	1941	Paraplegia, transient	Combined: obstruction of right iliac and spinal cord ischemia
Weisman and Adams[29]	1944	Paraplegia, permanent	Infarction of spinal cord
Weisman and Adams[29]	1944	Paraplegia, permanent	Common iliac obstruction
Weisman and Adams[29]	1944	Paraparesis, permanent	Common iliac obstruction
Weisman and Adams[29]	1944	Paraparesis, permanent	Aortic thrombosis
Ritvo and Votta[20]	1944	Paraplegia, permanent	Probable spinal cord ischemia
Thomas[25]	1945	Paraplegia (two episodes seven days apart, the second permanent)	Probable spinal cord ischemia
Cabot Case No. 33091[5]	1947	Paraplegia, transient	Spinal cord ischemia
Baer and Goldburgh[1]	1948	Paraplegia, transient	Spinal cord ischemia
Warren and McQuown[28]	1948	Paraplegia, permanent	Spinal cord ischemia

TABLE III. CAUSE OF PARALYSIS IN TWENTY-EIGHT CASES OF PARAPLEGIA AND PARAPARESIS DUE TO DISSECTING ANEURYSM COLLECTED FROM THE LITERATURE

PATHOLOGICAL BASIS	NO.	%
Ischemia of spinal cord	10	35.5
Ischemic neuropathy	11	39.5
Combined lesions	3	11.0
Undetermined	4	14.0

may have been greater than the intravascular cord pressure, thus preventing the escape of blood into the spinal fluid. In our case just the reverse picture occurred. One of the microscopic sections through the dorsal portion of the cord showed a break in the wall of the anterior spinal artery, but there was no sign of organization of the intraluminal clot, and we cannot be certain but that this finding was factitious.

SUMMARY

A case of dissecting aneurysm of the aorta is presented in which all the intercostal arteries were severed, causing hemorrhagic infarction of the spinal cord and complete motor and sensory paraplegia. To our knowledge it is the first such case reported in which spinal subarachnoid hemorrhage occurred.

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MYOCARDITIS AND FRIEDREICH'S ATAXIA

A Report of Two Cases

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FRIEDREICH'S ataxia is usually considered an heredofamilial degenerative disease exclusively of the central nervous system, in which the posterior columns, the spinocerebellar pathways, and the pyramidal tracts of the spinal cord are predominantly involved. Degenerative changes in the cerebellum may be present, while morbid alterations in the midbrain and cerebrum occur more rarely. The association of a chronic, diffuse, nonspecific myocarditis with Friedreich's ataxia has received surprisingly scant attention in the American and English literature, considering the frequency with which such an association may be discovered to exist.

In 1863, Friedreich[1] published the first description of the disorder which now bears his name. Of the six patients whom he reported, five who were studied ante mortem presented abnormalities of cardiac mechanism. Post-mortem findings were recorded in three cases; in two of these subjects there were gross and microscopic changes interpreted as fatty degeneration. In the third subject there was diffuse cardiac hypertrophy associated with mitral and aortic valvular disease, suggestively rheumatic in origin. Newton Pitt,[2] in 1887, was the first to draw particular attention to deranged cardiovascular function in individuals with Friedreich's ataxia. Among the necropsy findings in his case there was definite microscopic evidence of a chronic myocarditis, with congestion, patchy granular degeneration, fibrosis, and round cell infiltration. Two cusps of the aortic valve were adherent, and the margins of all cusps were slightly irregular and calcareous. No other valvular deformities were described. In 1946 Russell[3] collected from the French literature three additional cases of Friedreich's ataxia in which an interstitial myocarditis was found at autopsy. To these, she added four which came under her observation. Histopathologically, the process appeared to be chronic and progressive. Muscle destruction resulted from focal coagulative necrosis with collagenous tissue replacement, and there was compensatory hypertrophy of the surviving parenchymal fibers. Uneven, scanty interstitial infiltration with small lymphocytes and occasional polymorphonuclear

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cells earmarked a low-grade inflammatory element. Ellwood[4] recently reported a clinicopathologic study of two cases of Friedreich's ataxia with unusual cardiac complications. A diffuse interstitial myocardial fibrosis was found in one individual. The other manifested scarring of the mitral valve, slight atherosclerosis of the ascending aorta, and myocardial infarction; a true myocarditis was not reported in this patient.

From the clinical standpoint, abnormalities of cardiac mechanism and occasional terminal cardiac decompensation have been noted for eighty-five years in cases of Friedreich's ataxia. Such complications, frequently quite obscure in origin, have prompted several reports in French journals. There is a paucity of electrocardiographic studies of persons with Friedreich's disease, but those performed have yielded interesting results. Van Bogaert,[5] in four of eight cases thus investigated, found definite evidence of myocardial damage. Two patients presented T_1 and T_2 inversions, while two presented negativity of T_2 and T_3. In thirty-eight patients with Friedreich's disease, Evans and Wright[6] found twelve distinctly abnormal tracings and ten with suggestive irregularities. The definite abnormalities were preponderantly those of T-wave inversion in Leads I and II, singly or in various combinations with one another or with a negative T_3. There was a rather striking association of a positive family history of Friedreich's ataxia with abnormal electrocardiograms, and affected members of the same family tended to manifest similar electrocardiographic changes. Isolated case reports of electrocardiographic abnormalities associated with Friedreich's ataxia have appeared from time to time in the French literature.[7-10]

The etiology of the cardiopathy with which this disorder is occasionally attended is thoroughly obscure. The cardiac lesion has been attributed by some to degeneration of the vagal nuclei, resulting in sustained sympathetic hypertonia. Russell[3] ventures a toxic cause, as microscopic examination of the vagal nuclei in her patients disclosed no significant changes. It is difficult to visualize autonomic imbalance as a potential cause of a true myocarditis. If the cause be a toxin, its source remains as yet unidentified. In the foregoing case reports of Friedreich's disease associated with myocarditis, no significant inflammation was found in other organs, and it was not possible to demonstrate a possible focus of infection at necropsy. And whether or not an identical noxious agent is responsible for both the myocardial and central nervous system lesions is purely speculative.

We have recently had an opportunity to observe two patients with Friedreich's ataxia, in whom conspicuous clinical and electrocardiographic cardiac aberrations were apparent. A pathologic study was accomplished in one. The rarity with which the condition has been described seems to warrant the following case reports.

CASE REPORTS

CASE 1.—P. T., a 27-year-old Mexican man, was admitted to the State Psychopathic Hospital on July 24, 1947. The onset of the neurological disorder was dated to 1936, when the patient was struck on the right hip by a car. Subsequently he gradually developed weakness, poor coordination, and wasting of both legs. He had become unable to walk, and was incapacitated for work.

He had noted irregular heart action and palpitation since January, 1947. A communication from the family physician indicated that on June 2, 1947, the patient developed auricular fibrillation, with a fall of the arterial blood pressure to 60/0. At this time quinidine and digitalis were administered, and the blood pressure on June 16 was 130/70. In the history there was evidence neither of congenital heart disease nor of rheumatic fever. Family history was negative for similar illnesses.

The physical examination revealed a chronically ill man whose temperature was 99.0° F.; pulse rate, 100 per minute; respiratiratory rate, 20 per minute; and blood pressure, 100/80. Scattered moist râles were heard throughout both lungs. The heart was enlarged to about 3 cm. beyond the left midclavicular line in the fifth intercostal space. The rhythm was grossly irregular,

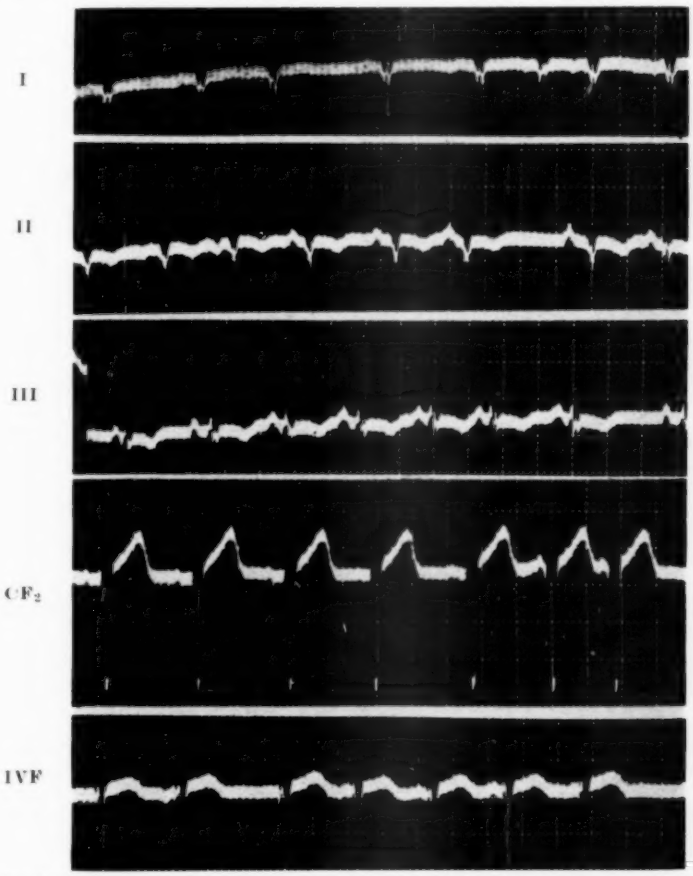

Fig. 1.—Electrocardiogram in Case 1 (P. T.), July 31, 1947, taken after reversion to sinus tachycardia, rate 110. Right axis deviation is present, and there are frequent supraventricular ectopic beats. Q_1 and Q_2 are deep, and QRS complexes are markedly notched in the limb leads. The T wave is flat in Lead I and negative in Leads II and III.

and rate at the apex was 140 per minute, compared with 100 at the wrist. There was a low-pitched apical murmur heard in early and middle diastole. The second pulmonary sound was loud and reduplicated. The speech had a halting, explosive quality. The muscles of the extremities were flaccid and atrophic. All movements were poorly executed, and marked ataxia was noted during tests for coordination. There was scoliosis of the thoracic vertebrae with the convexity to the right. A bilateral pes cavus was present and the deep, tendon reflexes were absent in the lower extremities. No pathologic reflexes were elicited. There was definite impairment of all modalities of sensation in the lower extremities. Cranial nerves were intact.

The laboratory studies revealed a red cell count of 4.66 million with 97 per cent hemoglobin. The white cells numbered 11,500 per cubic millimeter, and the differential count was essentially normal. Urinalysis revealed a specific gravity of 1.027, a trace of protein, and no sugar; microscopic examination revealed no abnormal constituents; blood Kahn and Kolmer tests were negative. Examination of the spinal fluid disclosed no abnormalities. The electrocardiogram (Fig. 1) revealed frequent supraventricular ectopic beats, with right axis deviation (axis 138°), and definite evidence of myocardial damage. Phonocardiographic study (Fig. 2) confirmed the presence of the apical diastolic murmur.

During hospitalization the patient was given nutritional support and physiotherapy. Since he showed no signs of cardiac decompensation, no cardiotonic drugs were administered. Two twenty-four hour courses of oral quinidine sulfate were given; a total dose of 1.0 Gm. on July 24, and a total dose of 1.5 Gm. on July 29. The second course succeeded in reverting the circus mechanism to sinus rhythm. On September 5 the patient complained of moderate epigastric pain and nausea. The symptoms soon disappeared, and the general condition remained about the same. At 5 A.M. on September 6 the patient suddenly vomited copious quantities of previously ingested food, and expired before emergency measures could be inaugurated.

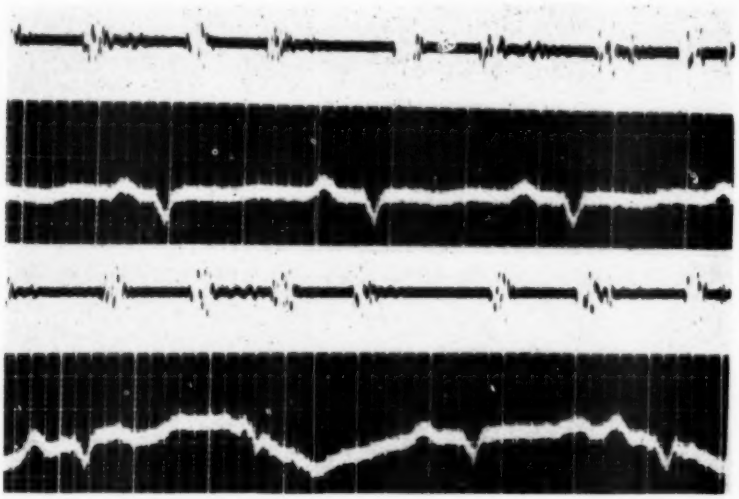

Fig. 2.—Phonocardiogram in Case 1, taken at same time as Fig. 1. The top tracing demonstrates the low-pitched apical murmur beginning immediately after the second sound and lasting through the middle of diastole. The bottom tracing shows a similar apical murmur with the patient recumbent on his left side.

Pathologic Findings.—At autopsy several points of interest relative to the clinical course were noted. The heart weighed 550 grams, and the epicardium was speckled with many small petechiae, which were most noticeable on the left ventricle and left atrium. The myocardium was reddish-brown in color, and in places was soft in consistency. The left ventricular wall measured 17 mm. in thickness, and the right measured 7 mm. in thickness. Both ventricular cavities were dilated. The endocardium was smooth, but there were several small grayish-red clots adherent to the apex of the left ventricle. The valve leaflets showed no gross abnormality. The coronary arteries showed no atherosclerosis, and no evidence of thrombosis or occlusion was found throughout their course. Microscopically the myocardium showed a diffuse interstitial fibrosis (Figs. 3 and 4). The myocardial fibers varied in size, and were rather widely separated by many strands of delicate fibrous connective tissue. Many of the fibers appeared larger than normal (Fig. 4). In some places there were a few lymphocytes and plasma cells scattered through the fibrous tissue.

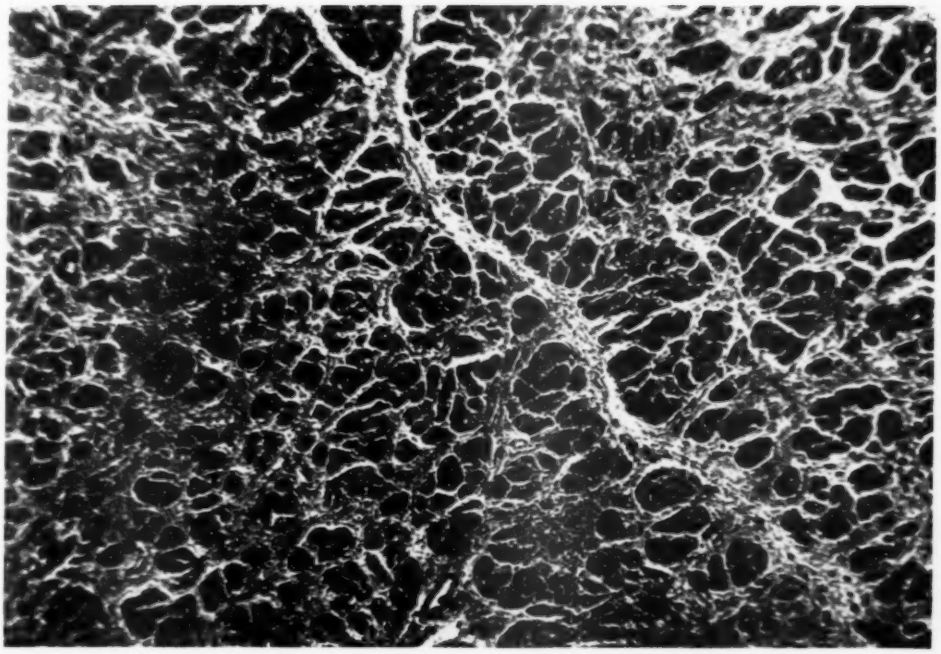

Fig. 3.—Section of myocardium in Case 1, under low magnification. Note the areas of degenerating myocardium with replacement by fibrous tissue. Some of the remaining muscle fibers show hypertrophy. The section is representative of the entire myocardium. (Hematoxylin and eosin stain, × 53.)

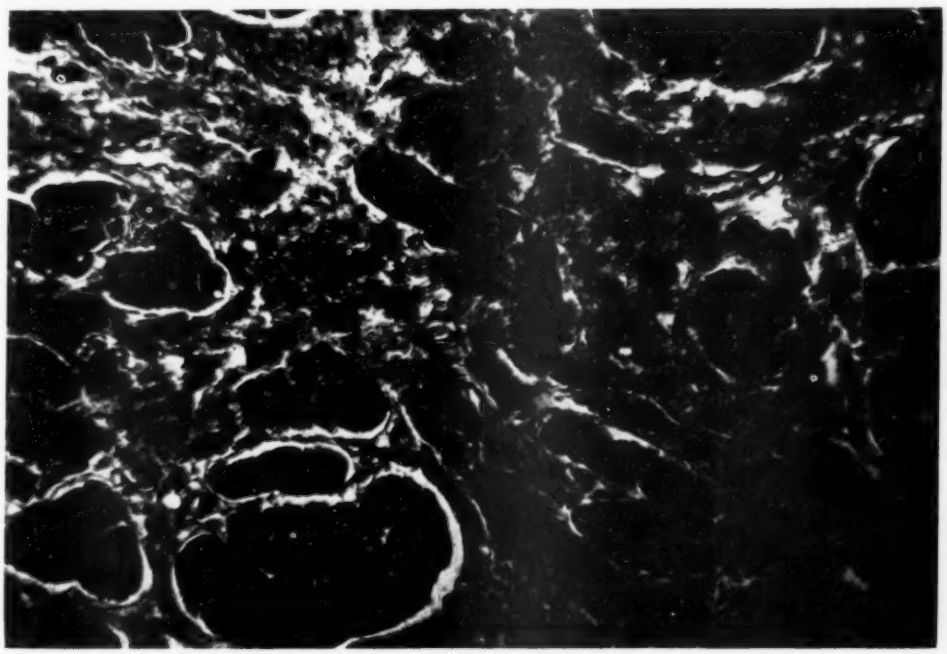

Fig. 4.—High-power magnification of the heart muscle in Case 1. The diffuse fibrosis enveloping the degenerating muscle fibers is conspicuous. Occasional small round cells can be seen. (Hematoxylin and eosin stain, × 300.)

The lungs weighed 1,150 and 950 grams, and on sectioning considerable pink fluid escaped from the cut surface. Microscopically, they showed pulmonary edema and many pigment-laden macrophages. The liver weighed 1,400 grams and showed slight chronic passive congestion. The right kidney weighed 150 grams, and the left weighed 170 grams. There was a small, old, stellate scar present on the cortex of the left kidney. There were no pathologic changes in the arterioles or glomeruli.

The brain weighed 1,450 grams and grossly showed no abnormality. The spinal cord was markedly flattened and thin in the anteroposterior dimensions. Grossly the cut section showed the dorsal columns to be thin and small. Microscopically the sections showed degeneration of the fasciculus gracilis, fasciculus cuneatus, and the dorsal spinocerebellar tracts. There was present considerable glial tissue with a whorled appearance, particularly in the fasciculus gracilis. No microscopic changes were noted in the cerebral hemispheres or in the cerebellum. Serial sections were not taken to demonstrate the vagal nuclei in their entirety, but no lesions were noted in this area.

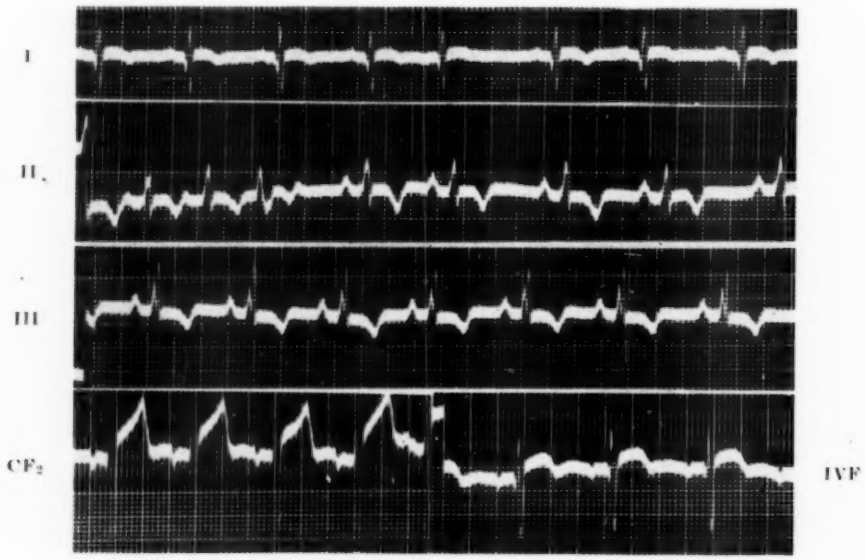

Fig. 5 *A*.—Electrocardiogram in Case 2 (C. H. C.), April 29, 1948. There is sinus rhythm at a rate of 88, with frequent atrial ectopic beats. A 2.0 mm. Q wave is present in Lead I, and a 1.0 mm. Q wave in Lead IVF. There is negativity of T_1, T_2, and T_3, and the RS-T segments are elevated in Leads CF_2 and IVF.

CASE 2.—C. H. C., a 28-year-old white man, was admitted to the State Psychopathic Hospital on March 19, 1947, and was hospitalized intermittently until June 1, 1948. Onset of symptoms was at the age of 14, when, following a fracture of the left leg, he failed to recover normal function despite good union. He noted progressive weakness of his legs, and several years later the weakness involved the arms and hands. For several months there had been numbness and tingling of the legs, feet, and hands. His speech became slower and scanning, and he had increasing awkwardness in writing. A tremor of the hands and feet was noted whenever he attempted to perform any act. The patient had been confined to a wheelchair since admission. There had been noted some dyspnea upon moderate exertion, but no other symptoms referable to the heart. There was no history of chorea, of prolonged fever, or of migratory polyarthritis. Several members of the family had high-arched feet similar to those of the patient, but there was no family history of mental or nervous illness.

On physical examination the patient was seen to be sthenic in habitus, and in no acute distress. The sensorium was clear, but speech was slow and slurred. Temperature was 98.6° F.; pulse rate, 100 per minute; respiratory rate, 20 per minute; and blood pressure, 130/80. The chest showed marked scoliosis with convexity to the right. The lungs appeared normal. The cardiac apical impulse was palpable in the fifth intercostal space, inside the midclavicular line. The heart was not enlarged, and contour appeared normal to percussion. There were no shocks or thrills. The heart tones were of fair quality, and occasional premature contractions were noted. Upon tachycardia induced by exercise, a short, low-pitched presystolic murmur was heard at the apex. No other murmurs were present. The second aortic and pulmonic sounds were equal in intensity. Abdomen, genitalia, and rectum were normal. There were high-arched feet bilaterally. Neurological examination showed that the patient was markedly ataxic, and unable to stand alone. Muscle strength of the upper and lower extremities was decreased. There was a generalized atrophy of the muscles of the lower extremities. A slow, coarse intention tremor involved all extremities. All coordinated movements were done with extreme difficulty. Deep reflexes of the upper extremities were markedly hypoactive, and patellar and ankle jerks could not be elicited. A bilateral positive Babinski sign was present. Abdominal and cremasteric reflexes were absent. Sensation to pain, touch, and temperature was intact. In the lower extremities, there was marked impairment of position and vibratory sensation. Nystagmus was present on right and left lateral gaze, but no other cranial-nerve abnormalities were elicited.

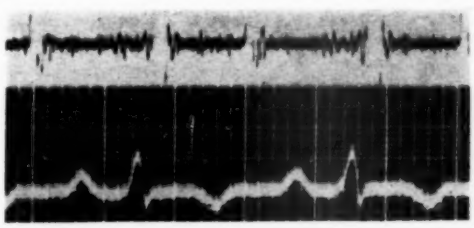

Fig. 5 *B*.—Phonocardiogram in Case 2 confirms the short apical presystolic murmur heard only during tachycardia.

Laboratory studies showed a red cell count of 5.32 million with 17.0 grams of hemoglobin. The white cell count was 10,600 per cubic millimeter, with a normal differential count. Urinalysis showed a specific gravity of 1.025, acid reaction, a faint trace of protein, and no sugar; microscopic examination showed no abnormal constituents. Reactions to blood Kahn and Kolmer tests were negative. An electroencephalogram, as well as skull and chest films, showed no abnormality. The spinal fluid was normal. An electrocardiogram (Fig. 5 *A*) showed marked alterations, and the phonocardiogram (Fig. 5 *B*) verified the presystolic murmur at the apex.

DISCUSSION

Despite the absence of a rheumatic history in Case 1, the diastolic apical murmur and atrial fibrillation strongly suggested the presence of mitral stenosis. However, the clinical suspicion of rheumatic heart disease was not substantiated at necropsy. The absence of valvular lesions was a striking finding, and exhaustive search failed to reveal any microscopic evidence that the myocardial changes were rheumatic in origin. The coronary arteries were widely patent, and showed no areas of atherosclerosis. Although the tracing in Fig. 1 shows only supraventricular ectopic beats, another tracing on this patient showed frequent impulses of ventricular origin. A sudden mechanism disorder such as ventricular fibrillation was considered the probable cause of the sudden death.

The microscopic appearance of the myocardium was similar to that described by Pitt[2] in a patient with Friedreich's ataxia, and by Russell[3] in her fourth case. There was collagenous tissue replacement of degenerating myocardium, with hypertrophy of some of the remaining muscle fibers. The diffuse fibrosis was prominent, with infiltration by a few small round cells. No acute necrotic changes were observed in the myocardium. There was a notable absence of the fatty degeneration described in some of the cases previously reported.

The clinical findings in Case 2 indicated that in all probability the cardiac lesion was also a myocarditis of the type associated with Friedreich's ataxia. There had been no episodes suggestive of rheumatic fever, and no symptoms or signs pointed to disease of the coronary arteries. The presystolic apical murmur was not conspicuous, and was heard only upon acceleration of the heart rate.

The electrocardiograms show marked abnormalities, and frequent auricular ectopic beats are present. There is a similarity in that both tracings show inversion of T_2 and T_3. In Case 2 the configuration in Lead I and Lead IVF was considered to be due to subepicardial involvement anteriorly. Several serial tracings taken over a period of three months showed no change, and there were no symptoms suggestive of a myocardial infarct.

Diastolic murmurs have been previously reported in patients with Friedreich's ataxia. The patient described by Pitt[2] had at the apex a "bruit, doubtfully presystolic," and at necropsy no mitral lesion was demonstrable. Debbasch, Calo, and Almanza[9] noted an apical presystolic murmur in a patient with Friedreich's ataxia, and two patients observed by Van Bogaert[5] had protodiastolic murmurs on exertion. Marked dilatation of the left ventricle relative to the mitral orifice is considered the most likely mechanism underlying the murmur heard in Case 1, as there was no necropsy evidence of valvular disease. Although mitral valvulitis cannot be excluded in the living patient, the fact that the murmur is heard only during tachycardia emphasizes the importance of the velocity of blood flow in its production. The functional aspect of certain apical diastolic murmurs has been stressed by Bramwell[11] and by Dechard and Beard.[12]

The frequent presence of myocarditis in Friedreich's disease appears to be well established, although its cause remains obscure. The rarity of its observation may well be due to failure to investigate this association. It seems to us that the diagnosis of Friedreich's ataxia should demand a thorough evaluation of the cardiac status. Limitation of activity and supportive measures may result in prolongation of life in patients in whom there is evidence of cardiopathy.

SUMMARY

The literature concerning myocarditis in Friedreich's ataxia is briefly reviewed.

Two cases of Friedreich's ataxia with marked electrocardiographic changes and apical diastolic murmurs are presented. Necropsy findings in one patient showed a diffuse interstitial myocarditis with nothing to identify a specific etiological basis. Both are presumed to be of the type associated with Friedreich's ataxia.

It is concluded that a thorough cardiac study is indicated in patients with Friedreich's disease.

The authors desire to express their appreciation to Jack R. Ewalt, M.D., Professor of Neuropsychiatry, for making this clinical material available; and to George R. Herrmann, M.D., for his aid and encouragement.

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PULMONARY HEMANGIOMA WITH PULMONARY ARTERY-AORTIC SEPTAL DEFECT

Attempted Roentgen Visualization by Catheterization of Brachial Artery and Basilic Veins

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DESPITE the fact that pulmonary hemangioma (arteriovenous fistula) is rarely encountered, this lesion assumes practical importance because of its curability by surgical means. Every effort should be made to establish the diagnosis, since delay in treatment may lead to pulmonary hemorrhage and death. The present case report illustrates such a catastrophe, in spite of the fact that the lesion was suspected and attempts were made to demonstrate it roentgenographically by both venous and arterial catheterization. This case is unique in that the patient also had a pulmonary artery-aortic septal defect.

CASE REPORT

J. P., a 20-year-old white man, was admitted to Jefferson Hospital on July 31, 1945. The essential features of his illness consisted of the presence of clubbing of the fingers and toes for fifteen years; cyanosis of the lips, fingers, and toes for ten years; dyspnea on exertion for ten years; pain in the left chest for the two months preceding admission; and two episodes of hemoptysis during the two months preceding admission.

There was no family history of congenital heart disease. The patient's mother had been treated for syphilis during the pregnancy; she had never had German measles.

At birth the patient was not a "blue baby." Cyanosis first became evident when the patient was about 4 years old, at which time a diagnosis of Ayerza's disease was suggested. The patient was studied at Hazleton State Hospital, Hazleton, Pa., and found to have a systolic murmur over the pulmonary artery, but no thrill. Roentgenograms of the chest revealed no enlargement of the heart, but the presence of a small shadow in the left upper lung, not associated with any hilar changes. The electrocardiogram revealed right axis deviation. The patient was studied many times during the following fifteen years, but the same findings persisted: absence of heart enlargement, normal pulse and blood pressure, inconstant systolic pulmonary murmur, accentuated second pulmonary sound, and an area of increased density in the upper left lung without hilar enlargement. The patient was sent to Jefferson Hospital by two of us (F. V. P. and J. F.) with the diagnosis of congenital heart disease and hemangioma of the lung.

Physical examination revealed the patient to be well developed physically and his nutritional status appeared good. Temperature, pulse, respirations, and blood pressure were normal. The abnormal physical findings were as follows: (1) cyanosis of face, lips, hands, and feet; (2) clubbing of fingers and toes; (3) thrill over the entire anterior chest wall; (4) dullness on percussion over an area just to the left of the aortic arch; (5) a loud, crescendo systolic murmur heard best over the pulmonic area but transmitted to the neck, left axilla, entire left chest, and to a lesser degree to the right chest.

From the Charlotte Drake Cardeza Foundation, Department of Medicine, and the Samuel D. Gross Surgical Division, Jefferson Hospital, Philadelphia, Pa., and the Hazleton State Hospital, Hazleton, Pa.

Blood studies revealed hemoglobin levels varying from 130 to 150 per cent, red blood cell counts from 7.1 to 8.3 million, hematocrit from 73 to 75, white blood cell counts from 5,000 to 11,000, and platelets from 60,000 to 150,000. A representative differential count was: polymorphonuclear cells, 86 per cent; basophiles, 1 per cent; lymphocytes, 11 per cent; and monocytes, 2 per cent. Examination of the sternal bone marrow revealed normal marrow hyperplasia but a distinct elevation in the percentage of normoblasts from a normal of 20 per cent to a level of 33 per cent. The sedimentation rate was found to be normal on three occasions. Repeated urinalyses, as well as kidney and liver function tests, were normal.

Roentgenograms of the chest (Figs. 1 and 2) revealed an oval shadow of increased density in the left upper lobe. The mass appeared homogeneous, had a smooth contour, and did not pulsate. The heart was normal in size, shape, and position. A test of swallowing function with barium revealed that the pulmonary mass was not located near the esophagus or the aorta. Lateral views of the thoracic and lumbar spine showed no abnormality of the vertebral bodies or their intervening spaces.

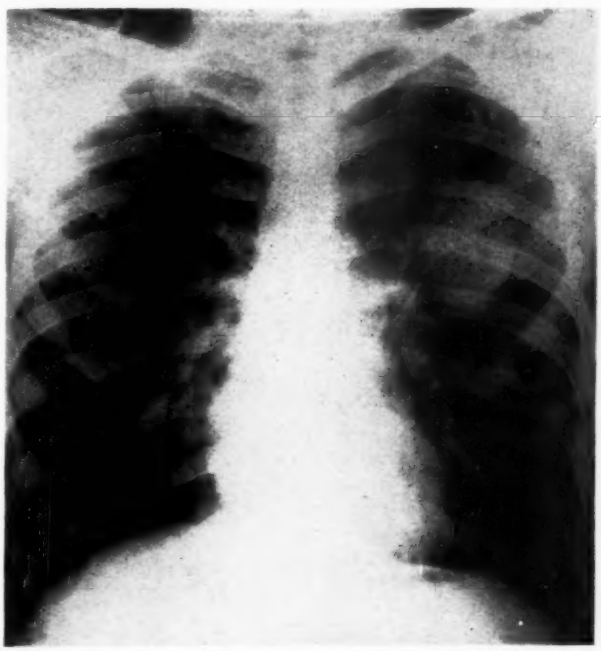

Fig. 1.—Plain roentgenogram of chest (anteroposterior view), showing oval shadow of arteriovenous aneurysm in left upper lobe.

The electrocardiogram showed marked right axis deviation, with notching and spreading of the P waves, suggesting auricular enlargement.

Bronchoscopy revealed definite narrowing of the left main bronchus due to encroachment on the anteroposterior diameter, so that the lumen of the bronchus presented its greater diameter in the coronal plane.

On Aug. 9, 1945, pulmonary arteriography was attempted. With local anesthesia, No. 8 F ureteral catheters were inserted (by F. B. W.) into the basilic veins of both arms and threaded under fluoroscopic guidance through the axillary and subclavian veins and superior vena cava into the right atrium. A scout film was then made, which showed the catheters in place. With the patient in proper position, 10 c.c. of 70 per cent Diodrast were injected simultaneously through each catheter, and two films of the chest were made at a two-second interval. These films showed

the right atrium and ventricle to be well filled, with dye passing through the pulmonary artery and out through the right and left pulmonary arteries into the small branches of each lung (Fig. 3). The branches surrounding the mass in the left upper lung were well visualized. The fact that at no time was any Diodrast seen in the left side of the heart or aorta on these films ruled out dextroposition of the aorta. The patient was then turned to a partial left anterior oblique position. A full oblique position was not obtainable because of the necessary placement of the arms. Again 10 c.c. of Diodrast were injected simultaneously through each catheter, and two exposures were made in quick succession. These films showed the right atrium, the right ventricle, and the pulmonary artery and its two main branches very well. Again there was no evidence of any opaque medium in the left ventricle or aorta. The outstanding feature demonstrated by these tests was a distinct dilatation of the pulmonary artery.

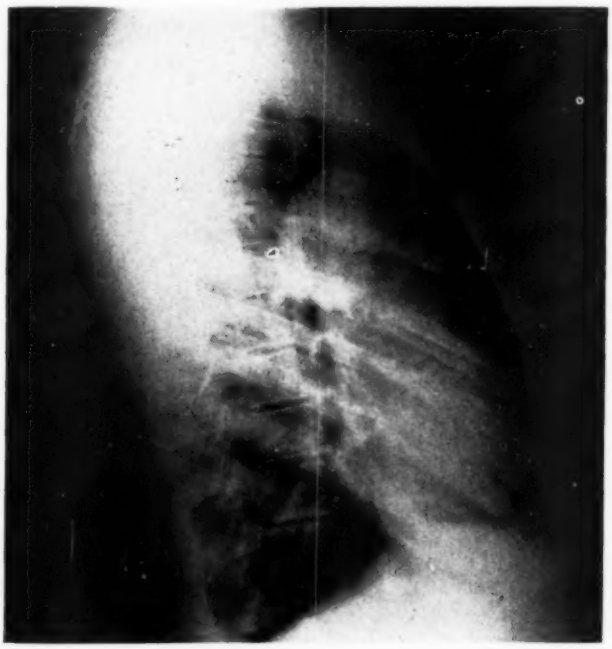

Fig. 2.—Lateral view of pulmonary arteriovenous aneurysm.

On Aug. 23, 1945, thoracic aortography was attempted. With the patient under local anesthesia, the right radial and ulnar arteries were exposed at their origin from the brachial artery. The radial artery was opened about one-fourth of an inch from its origin, and a No. 8 F ureteral catheter was quickly introduced upward through the brachial and subclavian arteries. Because of spasm of the artery about the catheter there was no leakage of blood at the site of introduction, but considerable force had to be exerted to advance the catheter. Under fluoroscopic vision it was noted that the catheter passed from the innominate artery into the common carotid. By elevating the patient's arm and rotating the catheter, it was possible to introduce it into the aorta and left ventricle. Ten cubic centimeters of 70 per cent Diodrast were injected through the catheter, and two films were taken at a two-second interval, starting immediately at the completion of injection. Unfortunately, the amount of Diodrast which could be injected through the catheter was too small to give clear definition of the aorta. Again 10 c.c. of Diodrast were injected, and two additional films were taken, as before. On one film there was faint visualization of the aorta, which was interpreted as showing evidence of some hypoplasia (Fig. 4).

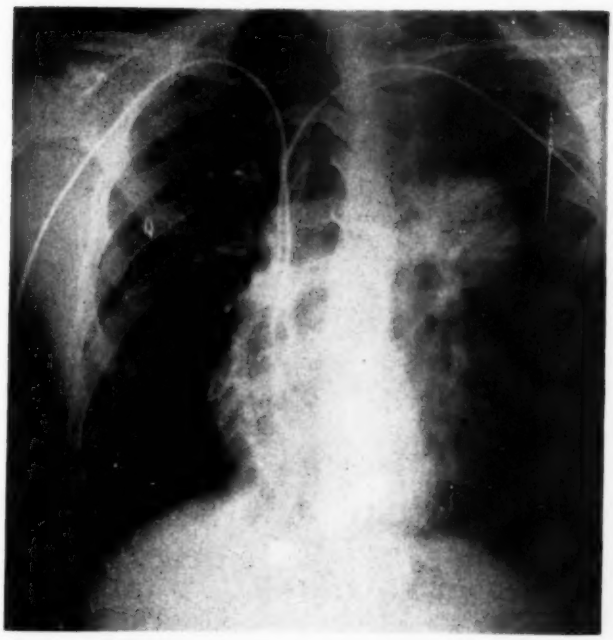

Fig. 3.—Pulmonary arteriogram, showing relation of mass in left upper lobe to the vessels.

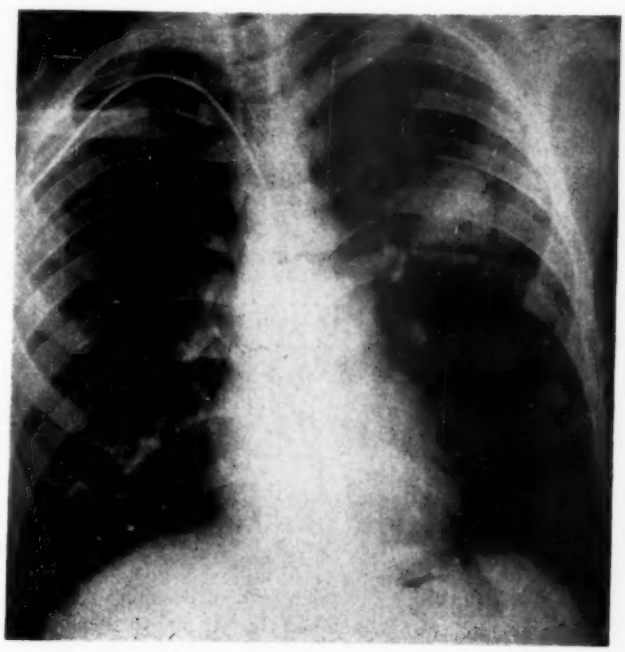

Fig. 4.—Attempted aortogram, by retrograde arterial catheterization.

The catheter remained in place about one-half hour, at the end of which time the right arm and hand were somewhat cooler than the left. On removal of the catheter, the radial artery was ligated on either side of the opening. Two hours later the right arm and hand were only slightly cooler than the opposite members, and no radial pulse was palpable at the wrist. Two days later both upper extremities were of equal warmth and a faint but definite radial pulse could be felt.

The patient was discharged on Sept. 4, 1945. He was advised to return for surgery, but because he felt well, he would not give consent to an operation. On May 11, 1947, the patient exerted himself unduly by pushing a stalled automobile. Within one hour he collapsed as a result of a large pulmonary hemorrhage, and was taken to the Hazleton State Hospital in a critical condition. In spite of all supportive measures, he expired. A post-mortem examination was performed.

Fig. 5.—Heart specimen, showing large foramen between aorta and pulmonary artery.

Post-mortem Findings (Hazleton State Hospital).—There was about 1.0 liter of free and clotted blood within the left pleural cavity, while none was present in the right. The left lung was of a dark bluish-red color, suggesting infiltration with blood throughout. With application of pressure to the midportion of the upper lobe, the pleural surface became raised at a point of apparent rupture, and a large amount of dark brown free and clotted blood escaped. On cut section, the left lung appeared hemorrhagic throughout, and the origin of the hemorrhage could be traced to a large, V-shaped, widened, cystic-like space filled with blood. The left lung had a weight of 3⅛ pounds, as compared with 1½ pounds for the right lung. There was slight hemorrhagic infiltration in the middle and upper lobes of the right lung.

Examination of the heart revealed a markedly hypertrophied right ventricle. On section, the right ventricle measured 2.5 cm. in thickness, as compared with a thickness of 1.5 cm. for the left ventricle. When the cardiac chambers and great vessels were opened, there was found a large oval communication between the aorta and pulmonary artery (Fig. 5). This foramen measured 3.2 cm. in its vertical diameter and 2.1 cm. in its horizontal diameter. The inferior margin of the foramen was 0.9 cm. above the upper free margin of the pulmonary valves and 0.1 cm. above the aortic valves. The intima was intact. All the valves were normal. There were no septal defects in the atria or ventricles.

Histologic examination of the left lung revealed extensive hemorrhages in all of the sections examined, with dilatation of the capillaries and marked hypertrophy of the medium-sized vessels. Tissue removed from the vicinity of the cystic spaces, at the origin of the rupture, revealed an irregular, cavernous appearance of the blood vessels, with papillary formation, as is seen in cavernous hemangioma.

The liver and spleen contained miliary granulomata.

DISCUSSION

The amenability to diagnosis and the ease of cure by surgery of pulmonary arteriovenous fistula have been the stimulus for an increasing number of reports of this rare lesion. The few case reports in the literature, however, warrant the accumulation of all available data in order to arrive at a more thorough understanding of this problem. For this reason the cases reported to date[1-16] are summarized in Table I.

Highly valid statistical data cannot be derived from the eighteen cases reported, but certain features seem outstanding. The condition is predominant in men. Although the lesion is congenital, the symptoms and signs usually do not become pronounced until the beginning of the third decade. Details of symptomatology and roentgenologic diagnosis have been adequately discussed in recent articles. The characteristic syndrome consists of cyanosis, clubbing of the fingers and toes, and polycythemia without abnormality of the heart; roentgenologic study reveals a lobulated mass of uniform density which may or may not pulsate under fluoroscopic observation. Either lung, or both lungs, may be involved, and the lesions are frequently multiple. Effective therapy consists in surgical extirpation of the involved portion of the lung, by lobectomy, pneumonectomy, or local excision. Ligation of the "feeder" artery may also result in improvement in properly selected cases. As in the case reported here, medical treatment is little more effective than no treatment at all, and the patient eventually will probably suffer a fatal pulmonary hemorrhage.

A noteworthy feature in the case reported here was the large foramen between the aorta and pulmonary artery. Such a defect must in itself be extremely rare, since Abbott[17] lists only ten analyzed cases of "communication between aorta and pulmonary artery" in her 1,000-case analysis, and White[18] and Taussig[19] list no additional cases. This lesion apparently represents an unusual variety of partial truncus arteriosus, in which the division of the aorta and pulmonary artery is incomplete but in which there is normal development of all the valves.

Since the effective pulmonary flow is decreased in the presence of a pulmonary arteriovenous fistula, it is logical to suppose that the communication between the aorta and pulmonary artery in this patient represented an attempt on the part of nature to overcome this circulatory handicap. It is evident that the shunt

TABLE I. CLINICAL FINDINGS, TREATMENT, AND RESULTS IN EIGHTEEN PREVIOUSLY REPORTED CASES AND IN THE PRESENT ADDITIONAL CASE OF PULMONARY ARTERIOVENOUS FISTULAS

AUTHORS	AGE AND SEX	CYANOSIS	CLUBBING	DYSPNEA	HEMOPTYSIS	BRUIT	CARDIAC ENLARGEMENT	POLYCYTHEMIA	ROENTGENOGRAM	LUNG INVOLVED	LESIONS	SURGICAL TREATMENT	RESULTS
Wilkins, 1917[1]	23, F.	+		+	+	+	+		+	R, L	3	0	Fatal hemorrhage; necropsy
Bowers, 1936[2]	2 days, M.	o	o	o	o	o	o			L		0	Died
Rodes, 1938[3]	25, M.	+	+	+	+	o	o	+	+	R, L	3	0	Fatal hemorrhage; necropsy
Smith and Horton, 1939[4]	46, M.	+	+	+	o	+	o	+	+	R	1	0	Living, 1946
Hepburn and Dauphinee, 1942[5]	23, F.	+	+	+	o	o	o	+	+	R	1	Pneumonectomy	Living and well
Goldman, 1943[6]	22, F.	+	+	+	o	+	o	+	+	L	1	0	Unimproved
Adams, Thornton, and Eichelberger, 1944[7]	24, M.	+	+	o	+	o	o	+	+	L	2	Pneumonectomy	Living and well
Jones and Thompson, 1944[8]	24, M.	+	+	o	o	+	o	+	+	R	1	Pneumonectomy	Living and well
Janes, 1944[9]	30, M.	+	o	o	+	+	o	o	+	R, L	3	Local excisions	Improved
Sisson, Murphy and Newman, 1945[10]	45, F.	+	+	+	+	+	+	+	+	R, L	2	0	Died, necropsy
Alexander, 1945[11]	41, M.	+	+	+	o	+		+	+	R, L		0	Died; coronary thrombosis
Makler and Zion, 1946[12]	20, M.	+	+	+	o	+	o	+	+	R, L	4	0	Unimproved
Beierwaltes and Byron, 1947[13]	27, F.	+	+	+	o	o	o	+	+	R	1	Lobectomy	Living and well
Burchell and Clagett, 1947[14]	20, M.	+	+	o	o	+	o	+	+	R	1	Lobectomy	Living and well
Watson, 1947[15a]	27, M.	+	o	o	o	o	o	o	+	R	1	Ligation of "feeder" artery	Improved
Watson, 1947[15b]	21, M.	+	+	+	o	o	o	+	+	R	1	Lobectomy	Living and well
Bisgard, 1947[16]	29, M.	+	+	+	o	+	o	+	+	R	1	Lobectomy	Living and well
Authors' case	20, M.	+	+	+	+	+	o	+	+	L	1	0	Fatal hemorrhage; necropsy

of blood from aorta to pulmonary artery produced pulmonary hypertension, as shown by the marked hypertrophy of the right ventricle at necropsy. This hypertension, however, rendered the patient's involved lung more susceptible to rupture. In addition, the shunt of blood from the aorta apparently became insufficient to overcome the reduction of effective pulmonary flow, since the patient developed polycythemia.

It is probable that this patient would have benefited from extirpation of the portion of lung bearing the arteriovenous fistula. The circulatory physiology would probably have reverted then to that obtaining in patent ductus arteriosus. Since the communication between aorta and pulmonary artery was not suspected during life, the postoperative result might have been confusing, indeed. Whether the large foramen could have been closed by operative intervention, had it been diagnosed and the procedure deemed beneficial, is a matter of the greatest conjecture.

The results of angiography by catheterization were disappointing in this patient. The information gained by the arterial catheterization hardly warranted the risk. Moreover, some of the findings were falsely interpreted. Some of the contrast medium injected into the left ventricle flowed through the pulmonary artery-aortic septal defect and into the lungs, thereby reducing the amount that should have gone into the aorta, which suggested an interpretation of hypoplastic aorta. The lumen of the catheter was too small to allow sufficiently rapid injection of the contrast medium. It is now definitely established that the Robb-Steinberg technique[20] of angiocardiography is the method of choice. However, in congenital heart disease, catheterization of the heart may yield valuable information when intracardiac pressures are taken and chemical analyses (oxygen tension of blood) made.

SUMMARY AND CONCLUSIONS

1. A case of pulmonary arteriovenous fistula associated with pulmonary artery-aortic septal defect is presented and discussed. The associated defect calls attention to the fact that other congenital vascular abnormalities should be looked for in patients with pulmonary arteriovenous aneurysms.

2. Attempted angiography by venous and arterial catheterizations proved interesting, but the Robb-Steinberg method would probably have been safer and more informative.

3. In the case presented, fatal pulmonary hemorrhage occurred as a result of delay in surgical intervention.

Since this article was submitted for publication, L. Dexter (Modern Medicine, February 15, 1949, p. 96) has reported that on one occasion aortic septal defect has been demonstrated by passage of the right heart catheter from the pulmonary artery into the aorta, but that in other suspected cases this could not be accomplished.

In addition, since this paper was submitted for publication, one of the authors (F.B.W.) performed angiocardiography by the Robb-Steinberg method on an additional patient suspected of having pulmonary hemangioma, with conclusive demonstration of the lesion in the right lung. Surgical therapy is planned.

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A CASE OF ANGINA PECTORIS PRECIPITATED CHIEFLY BY TOBACCO SMOKING AND MEALS

Report of a Case

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THE history of a patient with angina pectoris indicated that the attacks were brought about principally by eating and smoking. Since tobacco is an uncommon precipitating agent, and since the attacks were found to be accompanied by immediate reversible electrocardiographic changes, a detailed report of this particular case seemed justified.

CASE REPORT

In January, 1939, a 57-year-old typographer began to have chest pains, which rapidly became more severe. Initially, the attacks began with an oppressive pain across the back between the shoulders which radiated to the neck and both mandibles. He was occasionally subjected to spontaneous attacks at night. However, the seizures usually were attributable to one of the four classical reasons: cold, exertion, emotion, and heavy meals.

In the spring of 1944, the character and distribution of the pains changed. They were intensified, and shifted to the cardiac region, radiating from there toward the shoulders and the left lower jaw, and were often combined with a sensation of anguish. Otherwise, the patient seemed exceedingly neurolabile and frequently complained of diffuse dorsal and abdominal pains. These may have been associated with a duodenal lesion which was discovered later in his illness.

During the period of 1944 to 1946, he was given treatment at Sabbatsberg's Hospital on five separate occasions, and later in the Nylin Clinic at Södersjukhuset under the diagnosis of cardiosclerosis with angina pectoris, chronic gastritis, and neurosis.

When the patient was studied in October and November, 1946, it was learned that he had been unable to work for four months. Although he was able to walk almost without pain at a slow pace, rapid walking and heavy meals, in particular, provoked anginal attacks. An electrocardiogram showed a heart rate of 75 beats per minute. The P-Q interval was 0.16 second and the QRS interval 0.08 second. The R deflection showed a notch in the descending limb. There was left axis deviation. All RS-T segments were normal, and all T waves were positive. Tracings made in the supine and erect postures brought out no findings of interest. (Earlier electrocardiograms had shown transient A-V block, minor changes in the T-wave positivity, and definite changes of the posterior thoracic lead, indicating a posterior coronary syndrome.)

Because of the patient's insistent statements regarding a connection between pain and meals, especially when the latter contained semiliquid food, the following test was performed by one of us (O. G.). After a meal suitably prepared for the occasion, tracings were obtained at frequent intervals. Significant changes were noted to coincide with the occurrence of the customary subjective symptoms. These changes consisted of pronounced depressions of the RS-T segment in Leads I and II, the development of a diphasic T wave in Lead I, and a change in the configuration of the QRS complex in Lead III. As the pains subsided, the electrocardiogram gradually resumed the configuration it had when the patient was at rest. Thus, the test disclosed a latent anterior coronary insufficiency, apart from the old posterior one diagnosed previously.

From the Medical Clinic II of Södersjukhuset, Stockholm, Sweden. Headed by Professor Gustav Nylin.

Although the patient seemed to improve as a result of treatment and stated that he felt distinctly better, he found the hospital rules insupportable and was discharged (as on previous occasions) at his own request.

During the following winter and summer, he did surprisingly well and was able to work without too much inconvenience. He derived great help from nitroglycerin. Toward the fall of 1947, however, his troubles again rapidly increased. Anginal seizures of the same type as before made it increasingly difficult for him to get to work. He could now endure but slight exertion and was subjected to practically constant pains when exertion had been preceded by a meal.

When the patient was again studied in 1947, he related that he had noticed for a long time that his pains could be precipitated by tobacco smoking, and especially by the combination of smoking and exercise. When, a few years before, he had been able to walk around a block at a slow pace without any particular inconvenience, after smoking half a cigarette he was overcome half-way around the block by such severe pains that he could only return home with much difficulty after a long rest. The amount of tobacco required to precipitate an attack had gradually

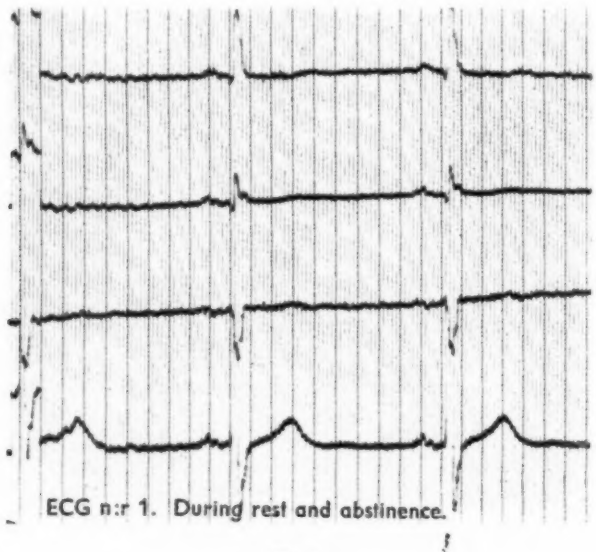

Fig. 1.

diminished. When our studies were made he was forced to smoke with great caution, since even one or two inhalations of smoke would cause serious inconvenience, although mere puffs without inhalation did not trouble him at all. In spite of the effects of smoking, he could not be prevailed upon to give up tobacco. When the patient himself was asked to evaluate the factors precipitating his attacks, he unconditionally put smoking first, meals second, and exercise third, the last one being the factor apparently most easily restricted.

Since in this particular case smoking was expected to accentuate the latent coronary insufficiency, one of us (B. v. A.) carried out a smoking test with electrocardiographic control on Nov. 3, 1947. The results follow.

With the patient recumbent after a rest, there were no symptoms. Blood pressure was 150/100. The control electrocardiogram (Fig. 1) showed a heart rate of 60 per minute, normal rhythm with a left axis deviation, P-Q intervals of 0.16 second, QRS duration of 0.08 second, normal RS-T segments, slightly flattened T waves in Leads II and III, and normal upright T waves in Lead IVF.

The patient then began to smoke a cigarette.

Clinical Observations.—

At 45 seconds moderate pain in both arms developed.
At 2 minutes the pain had increased and radiated to both jaws.
At 4 minutes the pain was accentuated.
At 5 minutes the blood pressure was 160/100.
At 6 minutes the pain began to subside.
At 8 minutes the pain was of no moment.
At 9 minutes the second cigarette was lighted.
At 10½ minutes the blood pressure was 175/100.
At 12 minutes no subjective symptoms were present.
At 15 minutes the blood pressure was 150/90. The patient felt cold and looked very pale. He seemed intoxicated.
At 17 minutes the test was discontinued after inhalation of the smoke of one and one-half cigarettes.
At 19 minutes the blood pressure was 145/85. There were no subjective symptoms, but the patient looked pale and his skin was cool to touch.

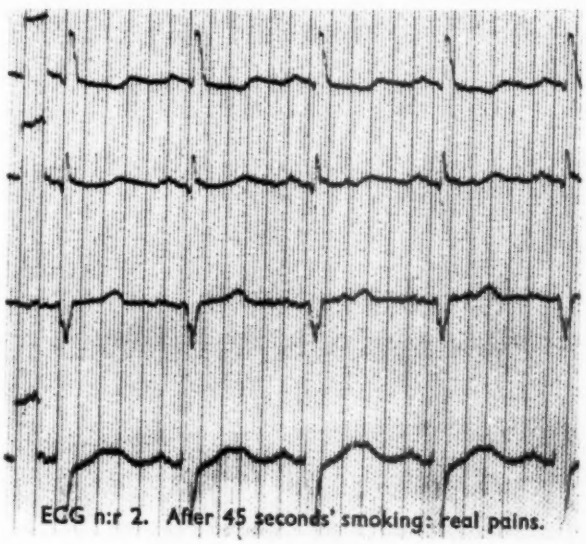

Fig. 2.

Electrocardiographic Observations.—

At 45 seconds after the beginning of the experiment (Fig. 2) the electrocardiogram showed a heart rate of 100 beats per minute, a normal rhythm, P-Q and QRS times unchanged, depression of the RS-T segment and downward displacement of the T wave of Lead I, upright T wave in Lead III, and flattening of the peak of the T wave in Lead IVF.
At 6 minutes (Fig. 3) the previously flattened T wave in Lead IVF became depressed and diphasic.

The anginal pain, felt as quickly as forty-five seconds after the smoking, disappeared after about ten minutes, as did the electrocardiographic changes. The record shows that the systolic blood pressure rose moderately in the initial stage, only to fall again later, while the diastolic pressure, which was initially constant, showed a later decrease.

A short while after the test, the patient took a few steps and was subjected to a severe anginal attack. This was quickly overcome by means of nitroglycerin and Oxyphyllin administered intravenously. He refused to stay at the hospital and set out for home. After walking for about fifteen minutes, he had a new attack, which was extremely violent. After resting for twenty

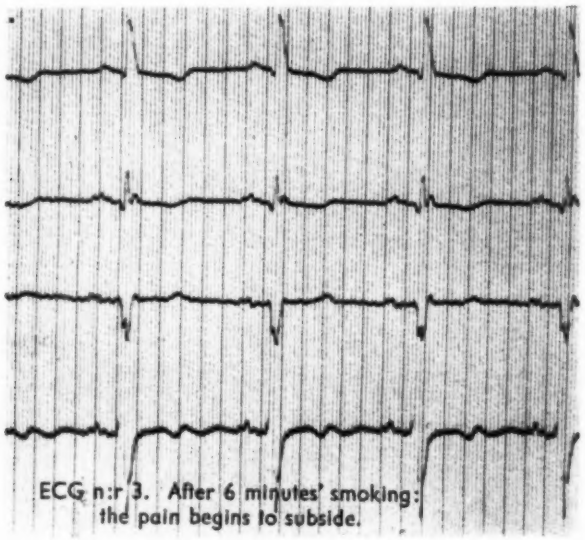

Fig. 3.

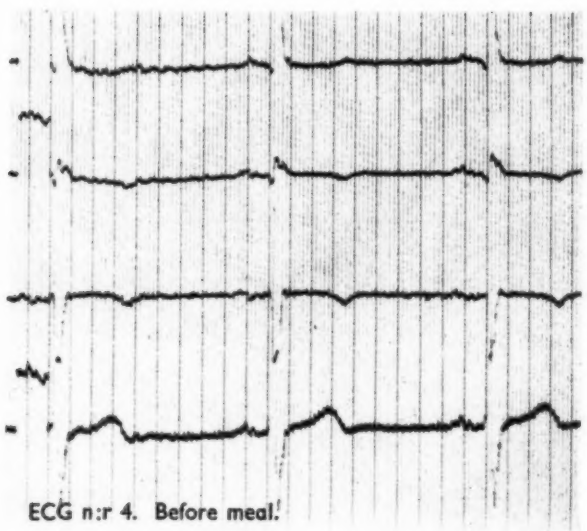

Fig. 4.

minutes, he was able to continue by car. However, because he lived on the fifth floor in a house without an elevator, he still had to submit to considerable exertion, with subsequent severe pains. After a light meal further deterioration occurred and he was brought back to the hospital in a severe anginal state which was eased only after energetic treatment.

During the physical examination at this admission, his manner was affected and he groaned aloud with pain. There were no symptoms of decompensation. The heart was clinically normal. The blood pressure was 150/100. The electrocardiogram showed the changes in the RS-T segments and T waves generally manifested during his attacks.

The following morning he ate a light meal consisting of porridge, milk, and three small sandwiches. After six minutes the expected attack set in and increased in intensity until twenty minutes had passed, when the attack was brought to an end by means of nitroglycerin. The same thing happened after he took a few puffs of a cigarette.

An electrocardiographic study was made during the attack induced by the meal just referred to. An electrocardiogram made before the meal (Fig. 4) was similar to previous control tracings except that the T wave was inverted in Lead II. The electrocardiogram made six minutes after the meal (Fig. 5) showed a depressed RS-T segment in Leads I and IVF, an inverted T wave in Lead I, and a diphasic T wave in Lead II.

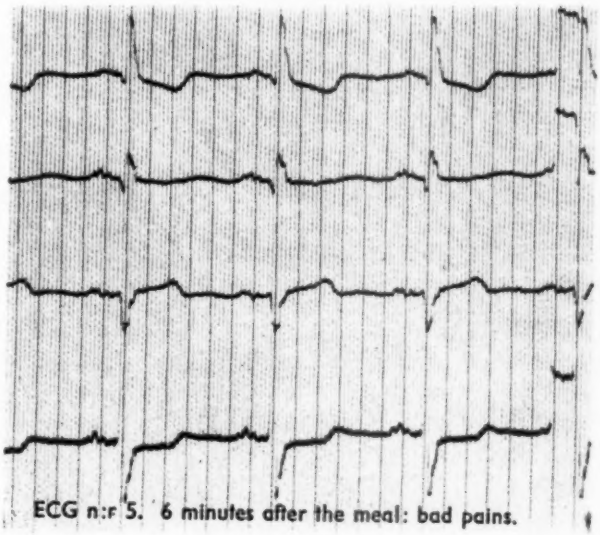

Fig. 5.

Following this electrocardiographic study, the patient remained in the hospital. During this period of observation it was found that the pulsations of the heart were rather small and that the volume of the heart was 910 c.c., which corresponds to 480 c.c. per square meter of body surface. No pulmonary congestion was present. Roentgenologic study of the stomach showed deformity of the duodenum.

DISCUSSION

We have been able to establish in this particular case that a meal as well as light tobacco smoking will precipitate distinct anginal attacks accompanied by definite but transient electrocardiographic changes. Heavy meals are assumed to cause anginal attacks as the result of dilatation of the stomach, which produces an increase in the minute volume of the circulation. This increase is stated to be capable of reaching a maximum of 30 to 40 per cent after one hour. A heavy meal is also thought to be able to set up reflexes which are capable of constricting the coronary vessels of predisposed persons. The combination of extra work and

a diminished blood supply to the heart furnishes a logical explanation for the anginal attacks which are occasionally precipitated by eating.

Tobacco smoking may also provoke angina pectoris, although this is by no means common. It is possible that the same mechanism operates in precipitating the less common instances of angina pectoris which are induced by smoking. This question will be discussed in some detail by V. Ahn in a later paper.

SUMMARY

A case of angina pectoris is described in which the attacks are chiefly precipitated by tobacco smoking and meals, as well as by the more usual precipitating factors.

Electrocardiograms showing reversible changes characteristic of temporary insufficiency of the coronary arteries, were recorded during an attack of angina pectoris induced by eating and during an attack induced by smoking.

MITRAL STENOSIS AND INSUFFICIENCY PRODUCED BY CARDIAC "MYXOMA"

MAY S. WEINSTEIN, M.D., AND JUSTIN E. ARATA, M.D.

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RARE as cardiac tumors are, it is surprising to discover in reviewing the literature how many have been reported. At present they remain largely a matter of academic interest, but with the recent great impetus in cardiac surgery, the possibility of surgical removal of the benign heart tumor does not now seem remote. The report of a case is offered in the hope that, as more cases are made public, a clinical picture may develop to facilitate the ante-mortem diagnosis.

CASE REPORT

Clinical History.—A 64-year-old doctor's wife entered the hospital (47-3484) with a two-year history of progressive weakness and a weight loss of thirty to thirty-five pounds. She had had intermittent episodes of night sweats, which had become more severe in the last two months. For two weeks prior to admission she had experienced chilly sensations, which usually occurred in the late afternoon and were followed by a low-grade fever. For two months previously there was epigastric distress described as an "emptiness in the pit of the stomach." This was not related to the ingestion of food, and occurred shortly after the patient arose in the morning and was relieved when she was lying down. The patient had visited several clinics, and except for cystitis, which had been diagnosed two years before and had disappeared on sulfonamide therapy, nothing had been found to explain her weakness and weight loss.

In the past history the patient had suffered from "infectious rheumatism" at the age of 16, and brucellosis at the age of 47.

Physical examination on admission revealed a woman apparently chronically ill and showing evidence of considerable weight loss. The temperature was 99, the pulse 84, and the respiratory rate 20. The positive findings were limited to the heart and abdomen. There was a diffuse precordial impulse, and the point of maximum intensity was in the fifth intercostal space, 2.0 cm. outside the midclavicular line. The rate was 84 and the rhythm regular. There was a soft presystolic and a harsh systolic murmur at the mitral area, and the second aortic sound was accentuated. The blood pressure was 90/60. The right kidney was easily palpable, not enlarged, and freely movable.

Urinalysis was negative except for 6 to 8 white cells. There were 12 Gm. of hemoglobin and the red count was 4.7 million. The white cells numbered 7.3 thousand, with 59 per cent neutrophiles, 40 per cent lymphocytes, and 1 per cent eosinophiles. The Mazzini test for syphilis, and an agglutination test for brucellosis were negative. The stool culture was noninformative, and the blood culture was sterile. A complete x-ray examination of the gastrointestinal tract was said to be negative. An intravenous pyelogram showed a low-lying right kidney whose function, however, was good. An x-ray examination of the chest uncovered moderate cardiac enlargement with "mitralization" of the left border; the lung fields were clear.

During her eight-day hospital stay the patient occasionally had an afternoon rise of temperature, which never exceeded 100.4° Fahrenheit. Although she was ambulatory, she com-

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plained of weakness. The clinical impression was that of rheumatic heart disease with mitral stenosis and insufficiency. No diagnosis was made to explain her leading symptoms.

One month later, the woman re-entered the hospital with complaints of dyspnea and a tickling sensation in the throat causing paroxysms of coughing. These symptoms were intensified when she lay on her back or left side, and were relieved when she lay on the right side. Her family physician stated that the patient had developed cardiac decompensation at home but had responded well to digitalis medication.

The temperature was 98, the pulse 80, the respiratory rate 20, and the blood pressure 80/50. The physical examination was essentially the same as on the previous admission.

Fig. 1.—Heart. Left atrium and ventricle incised to expose pedunculated "myxoma" extending into the ventricle from above the mitral ring area.

The urine showed a heavy trace of albumin, with 5 to 10 white cells. The hemoglobin was 12.0 grams; the red count, 4.1 million; and the white cells numbered 8.0 thousand, with 73 per cent neutrophiles, 26 per cent lymphocytes and 1 per cent eosinophiles. The agglutination test for brucellosis was repeated, and now was positive in a dilution of 1:40. An electrocardiogram on the twentieth hospital day showed flat T waves in Leads I and IV, and inversion of the T waves in Leads II and III. The urea nitrogen was 59 mg., and a repetition of the intravenous pyelogram now revealed poor function of both kidneys, particularly of the right.

The patient's condition remained relatively unchanged until the seventeenth hospital day, when she began to develop edema of the lower extremities, râles at the lung bases, and a palpable

liver, in spite of treatment with digitalis and diuretics. The next day she suffered a sudden attack of syncope, from which she recovered within a few minutes. On the thirty-seventh day she complained of severe pain in the left leg, which was noted to be cold, mottled, and pulseless. Heparin administration was begun immediately, but the patient continued to sink rapidly and died in obvious heart failure thirty-nine days after having been admitted to the hospital for the second time.

Necropsy.—A post-mortem examination (47-A-063) was done two hours after death, and the findings were chiefly related to the heart. That organ weighed 375 grams and measured 16 cm. in the greatest transverse diameter. The tricuspid ring was 11.5 cm. in circumference and the leaflets were slightly thickened at their free edges; the cords appeared natural. The pulmonic valve was 8.0 cm. in circumference. In the smaller branches of the pulmonary artery were numerous small emboli, well-adherent to the arterial wall.

The left atrium was dilated, and attached to and extending from its endocardium above the posterior commissure of the mitral valve was a polypoid mass, 6.0 by 5.0 by 3.0 cm. (Fig. 1.)

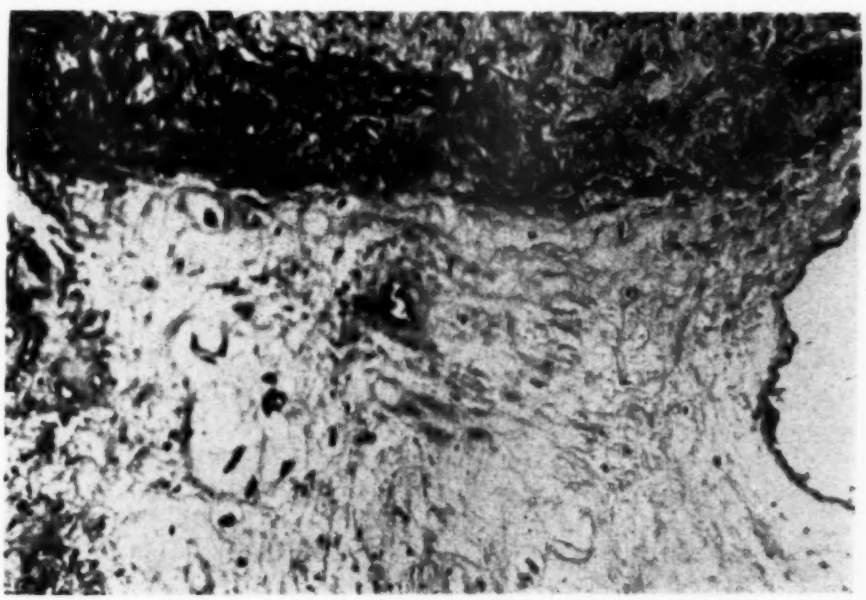

Fig. 2.—Heart. Photomicrograph of junction of atrial wall (horizontal, broad, dark area, above), and base of "myxoma." The clear spaces with small, deep-staining nuclei are identified as myxoid cells.

This reached into the left ventricle to within 3.0 cm. of the apex. The base of the tumor was 1.5 cm. wide.

There was an embolus in the left femoral artery and a thrombus in the accompanying vein directly adjacent to the artery. This was the cause of the incipient gangrene of the lower limb.

Microscopically, the cardiac tumor was largely formed of relatively immature mesenchymal elements. Centrally, there were large areas of thrombus. Adjacent to the latter there was granulation tissue in which were large mononuclear cells laden with hemosiderin. In the base of the mass the loose tissues were filled with an indefinitely outlined basophilic material similar to that seen in myxoid tissues. Some cells closer to the base were surrounded by large spaces with a thin rim of basophilic material. Lying within the spaces were single, round-to-oval eosinophilic refractile masses containing one to eight small, round, relatively solid nuclei (Fig. 2). There was scarring of the inner portion of the atrial muscle adjacent to the attachment of the tumor. At the center of the base of the mass was a small artery continuing into the endocardium.

DISCUSSION

Much discussion has centered about the question of whether the type of tumor discussed here originates from primitive mesenchyme or whether it is formed from the organization of a thrombus. Among the authors who believe that these tumors are true neoplasms and arise from mesenchymal tissue are Ewing,[2] Yater,[3] Strauss,[4] Ribbert,[5] and Brown.[6] Ribbert maintains that rests of embryonal mucoid tissue may persist in the heart, generally near the rim of the fossa ovalis, the most frequent site of origin of the myxoma. In refuting the thrombus theory, Brown states that organization of thrombi occurs most often in the peripheral vessels and in the ventricles; they are rarely the site of myxomas. He also points out that the occurrence of myxomas in otherwise normal hearts favors the neoplastic theory.

The proponents of the thrombus theory include Thorel,[7] Warthin,[8] Jaleski,[9] Maun,[10] and Anderson and Dmytryk.[11] In reporting his case, Maun presented several reasons why the tumor is of thrombotic origin and not a true myxoma. The chief features were the presence of injury to the auricular wall at the site of attachment of the pedicle, and the histologic picture of a thrombus which failed to show the microscopic picture of a myxoma or to stain for mucin.

In a recent extensive monograph, Mahaim[12] straddles the dilemma by speaking of "myxomatous polyps."

In our case, the finding of myxomatous elements near the base of the tumor surrounded by thrombotic material suggests a true primary neoplasm on which there has been superimposed thrombus formation.

Yater[3] quoted Mandelstamm,[13] who collected 143 cases of primary tumors of the heart. The greater number of these, 117, were benign, and were chiefly myxomas. There were, however, twenty-six which were malignant, mostly sarcomas. In the 214 cases assembled by Yater, the myxomas led in frequency, with seventy-five of that type. There were twenty-five tumors classed as fibromas, forty-six as sarcomas, forty-one as rhabdomyomas, and twenty-one as lipomas. The six others included instances of lymphangio-endothelioma, hemangio-endothelioma, leiomyoma, and rhabdomyosarcoma. Lymburner,[14] quoted by Barnes, Beaver, and Snell[15] in 1934, found 226 cases of primary tumors of the heart in the literature. He added four cases of his own, collected from 8,550 post-mortem examinations at the Mayo Clinic. Of interest is the fact that there were fifty-two cases of metastatic tumors of the heart in the same series of necropsies.

The symptomatology of cardiac tumors is extremely variable, and depends on the type of tumor, size, and location. While there are no symptoms which are characteristic, certain abnormalities should make the examining physician suspicious of their presence. Abnormalities of cardiac rhythm, particularly variable degrees of heart block, sudden onset of congestive heart failure in the absence of previous heart disease, or bloody pericardial effusion should suggest the presence of a neoplastic cardiac process.[16] In any individual with a known malignant tumor, the appearance of any of these symptoms or signs tends to implicate metastasis to the heart. In 1942 Doane and Pressman[17] reviewed nine-

teen cases of metastatic cardiac tumors that had been diagnosed before death and added one of their own. Among these twenty cases the right auricle was the site of metastasis in nine instances. These workers emphasize that whenever the right side of the heart is involved, there is great likelihood that the interventricular septum will also be attacked by the same process, thus embarrassing the conduction system.

A primary malignant tumor of the heart should be considered whenever the signs already described are present, and if other causes for such cardiac dysfunction can reasonably be ruled out. There are only two reports of primary malignant cardiac tumor diagnosed ante mortem. The case of Barnes, Beaver, and Snell[15] was uncovered by the coexistence of signs of acute pericarditis, the sudden appearance of heart block, and the presence of metastasis to the muscles of the shoulder girdle. Shelburne's case[18] was diagnosed before death from the rapid accumulation of bloody pericardial effusion, after all other causes for this condition had been excluded.

Credit for the only ante-mortem diagnosis of a primary benign heart tumor usually is given to Pavalowsky, in 1893.[23] However, this has been challenged by Strauss[4] and others.

The most common benign cardiac tumor is the myxoma, which arises most frequently in the left auricle in the region of the fossa ovalis. It often attains large size, and, because of its location and pedunculated character, produces symptoms most commonly diagnosed as mitral valvular disease.[19-23] In 1941, Lisa, Hirschhorn, and Hart[24] reviewed seventy-two cases of primary cardiac tumors already reported in the literature. More than half the benign tumors were myxomas, and, in turn, in more than half of these an ante-mortem diagnosis of mitral stenosis was made. This is in contrast to the single instance of a diagnosis of mitral stenosis in the group of primary malignant heart neoplasms. Several cases of myxomas have been reported with the ante-mortem diagnosis of subacute bacterial endocarditis, because of the mitral murmur and embolic phenomena.[6] In our case, the diagnosis of rheumatic heart disease with mitral stenosis and insufficiency was made, and subacute bacterial endocarditis was thought of because of the persistence of low-grade fever.

How these cases can be differentiated from true mitral valvular disease still remains a problem. An awareness of these tumors, despite their rarity, is still the best clinical tool. Yater,[3] among others, maintains that a negative rheumatic history is helpful. This may be of little value since it is well known that an established endocarditis may exist without any history of an acute attack. Of greater value are the following: (1) modification of the character of the apical murmur with change of bodily position of the patient; (2) sudden attacks of syncope, dyspnea, or cyanosis on change of position; (3) abnormalities of the x-ray cardiac silhouette,[26] particularly rapid increase in size of the right side of the heart; (4) rapid onset of progressive heart failure in a patient with no known cardiac disease who does not respond well to digitalis; and (5) sudden appearance of cardiac murmurs in a patient who has been under medical supervision and in whom no murmurs have been noted previously.

It is well, therefore, to remember that cardiac tumors exist, and their presence should be suspected in those patients with mitral stenosis which does not behave in typical fashion. It is possible that, as the demand for a more positive method of diagnosing cardiac tumors increases, a laboratory technique will be devised to fulfill the need. Although angiocardiography has not been reported to have been used for visualization of these lesions, it may prove to be an additional implement in the armamentarium for the diagnosis of cardiac tumors.[27]

SUMMARY

A case of a myxoma of the left auricle, diagnosed ante mortem as rheumatic heart disease with mitral stenosis and insufficiency, is reported.

Autopsy findings are presented, with a brief discussion as to the character of these tumors.

A review of the literature on incidence and frequency of cardiac tumors is given.

Symptomatology of cardiac tumors is discussed, with special reference to those features aiding in the ante-mortem diagnosis of the most common benign type, the myxoma.

We are indebted to Dr. N. L. Salon for furnishing the clinical history, and to Mrs. Grace Brooks for technical assistance.

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BRUCELLA MELITENSIS ENDOCARDITIS

Report of a Case

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THE occurrence of endocarditis as a complication of Brucella infection is rare. A review of the literature by DeGowin and associates[1] in 1945 revealed only sixteen cases, one of which was caused by *Br. suis*, and the others by either *Br. abortus* or *Br. melitensis*. Since that time only one additional case has been reported,[2] bringing the total number of cases to seventeen. Call and associates[3] noted that in all reported cases except four there was either historical or pathologic evidence of previous rheumatic fever. The infection occurred on a congenital bicuspid aortic valve in one case and on apparently normal valves in only two instances. The case to be reported, although it does not fulfill completely the rigid specifications of Spink and Nelson,[4] since the post-mortem cultures from the involved valve were contaminated, is felt, by virtue of the positive blood cultures for *Br. melitensis* and a demonstrated vegetation, to qualify as another example of endocarditis caused by Brucella organisms.

CASE REPORT

The patient, a 31-year-old white man, was admitted to the Albany Hospital on July 18, 1943, with the chief complaint of malaise, fever, and dizziness of one week's duration. At the age of 11 years the patient was placed in bed for six months for an attack of acute rheumatic fever. He had been without complaints since then except for occasional attacks of palpitation. Five months prior to the present illness, the patient experienced pain in the precordium. He was digitalized by his local physician, and returned to work in ten days. Three weeks prior to admission, he noted the onset of weakness and fatigue, with diaphoresis. One week prior to admission he complained of malaise, aching bones, fever, and dizziness. Four days before admission he noted migrating pain in both ankles and feet. There was an eighteen-pound weight loss in the three weeks prior to admission.

The past history, family history, and systemic review were noncontributory, except that the patient had been reared on a farm.

On physical examination his temperature was 100° F., his pulse 80, his respiratory rate 22, and his blood pressure 170/90. The head and neck were normal. The heart was enlarged to the left and had a normal sinus rhythm. At the apex a systolic murmur and a rumbling presystolic murmur were heard, with accentuation of the mitral first sound. At the aortic area a rough systolic murmur and a blowing diastolic murmur were heard. Except for moderate tenderness in the metatarsal joints, there were no unusual physical findings. No petechiae were noted.

Significant laboratory findings included 40 red cells in the urine sediment. Three blood cultures were negative. The Wassermann test was negative.

The patient was discharged after twenty-four hours, against the advice of his physician, with a tentative diagnosis of rheumatic heart disease and subacute bacterial endocarditis, with focal embolic nephritis.

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The patient was next seen eight months later, in March, 1944. Four months prior to admission he had been troubled by occasional diarrhea, with cramps, and had had daily elevations of temperature ranging from 99° to 103° Fahrenheit. There were no further complaints of arthritis or arthralgia. On physical examination the temperature was 102°, the pulse 120, the respirations 25, and the blood pressure 140/50. The physical findings were approximately the same as on the previous admission, except for an increase in the intensity of the sounds heard at the aortic area and moderate tenderness in both upper abdominal quadrants. Again no petechiae were noted.

No red cells were found in the urine on this admission. Agglutination tests for typhoid, paratyphoid, and Proteus OX 19 were negative. Blood cultures and stool cultures were negative. On admission, *Br. abortus* was agglutinated in a titer of 1:40, and four days later at 1:80.

The patient's temperature fell to normal gradually and he was discharged five days after admission.

The patient's third admission took place two weeks later. His complaints were of continued fever, chest pain, and discomfort in the shoulder joints. There had been frequent episodes of epistaxis.

On physical examination the temperature was 99.4° F., the pulse 120, the respirations 32, and the blood pressure 130/70. At this time it was thought that a pericardial friction rub was heard, and that the spleen was slightly enlarged. There had been no other significant change since the previous admission.

The electrocardiogram on admission was normal. A microcytic anemia and an elevated sedimentation rate were present. Blood cultures taken on admission and three, four, five, and seven weeks thereafter were negative. However, two blood cultures taken on successive days one month after admission were positive for *Br. melitensis*, as was one culture taken six weeks after admission. Three weeks after admission *Br. melitensis* was agglutinated in a titer of 1:160. At all times the white cell count and urine were normal.

Clinically, the patient's course was progressively downhill. Daily temperature elevations occurred. The patient was digitalized. The spleen gradually grew larger, conjunctival petechiae appeared, and the fingers became clubbed. The diastolic murmur at the aortic area increased in intensity. One month after admission the patient had a three-day episode of generalized arthralgia, which responded to salicylates. Since penicillin was not available, only supportive therapy and blood transfusions were utilized. The patient died in May, 1944, approximately two months after his final admission.

Necropsy.—Chronic passive congestion of all viscera was noted, but specific pathologic change was seen only in the heart.

The heart was enlarged, weighing 690 grams, and all its chambers, especially the left ventricle, were dilated. The epicardial surfaces were covered with a thin layer of fibrinous exudate, evidence of acute pericarditis. The coronary arteries and their branches were not enlarged or inflamed, and their walls were thin and pliable.

When the heart was sectioned, the left ventricular myocardium was found to be dull beefy-red in color, soft and flabby in consistency, and markedly hypertrophied, measuring from 1.8 to 2.0 cm. in thickness. The right ventricular myocardium was not remarkable. The mural endocardium was generally smooth and glistening, and the tricuspid, pulmonic, and mitral valves were thin, delicate, and pliable.

The aortic valve showed marked pathologic changes. The anterior or middle cusp of this valve was almost completely hidden beneath a large, irregularly ovoid, friable vegetation, the surface of which was covered by a thin layer of freshly clotted blood. The right and left posterior cusps were contracted and shortened and their surfaces were nodular as a result of replacement by dense, old, fibrous tissue. At their edges they blended into the large, friable, fibrinous vegetation on the anterior cusp. From these old sclerotic changes it is obvious that the aortic valve was the site of a diffuse inflammatory process at some previous time; it seems probable that the inflammatory process was rheumatic in character.

Careful inspection of the anterior cusp with the large, fresh vegetation showed that this structure was also thickened and sclerosed, as was the aortic ring, which was markedly narrowed, measuring only 6.0 cm. in circumference. Beneath the vegetation itself the cusp was ulcerated and in one place actually perforated.

The aortic valve was, therefore, the seat of two pathologic processes: one, an old, healed inflammatory lesion, presumably rheumatic, with fibrosis and shortening of the cusps, and resulting stenosis; the other, a recent superimposed acute active infectious process, with ulceration and perforation of the anterior cusp and the formation of a large, fibrinous vegetation or thrombus over the affected cusp.

Histologic examination of the aortic cusps and the aortic ring showed evidence of an old, healed inflammatory process, with much fibrosis, especially of the cusps themselves. In addition, the anterior cusp was the seat of a superimposed acute suppurative inflammatory process, with ulceration and acute thrombus formation. This lesion was unquestionably infectious in nature.

Sections from the inflamed and ulcerated anterior cusp showed the large, friable vegetation observed grossly. The vegetation was a typical recent thrombus, being composed of masses of agglutinated platelets intermeshed with strands of fibrin and infiltrated with large numbers of neutrophiles.

Sections stained by the classical Gram-Weigert method failed to disclose the presence of bacteria in the thrombus. However, since the microorganisms isolated from the heart's blood at autopsy, *Br. melitensis*, were gram-negative bacilli, the same sections from the thrombosed cusp were restained by the Gram-Weigert method but were not decolorized. These sections showed innumerable minute, short, well-stained coccobacilli which were distributed throughout many portions of the thrombus. They were present either singly or in small and large groups or clumps. Their morphology was typical of Brucella and the fact that they lost their deep purple stain when the Gram-Weigert preparations were decolorized definitely indicated that they were actually gram-negative bacilli.

In order to check these findings by another method designed to stain bacteria in tissues, the same sections were stained by McCallum's modification of Goodpasture's method for the demonstration of both gram-positive and gram-negative bacteria in tissues. In these preparations, careful examination disclosed the presence of the same minute, short coccobacilli which morphologically resembled *Br. melitensis*. As in the other preparations, they were present chiefly in small groups or clusters. In these preparations, however, they took the red stain, which, in this technique, indicates specifically their gram-negative character.

The finding, deeply embedded in the thrombus, of great numbers of minute, short, coccobacilli proved quite conclusively their etiological relation to the acute ulcerative valvulitis of the affected aortic cusp. The morphologic resemblance of these microorganisms to *Br. abortus*, the bacterium isolated from the heart's blood taken at necropsy, together with their proved gram-negative character, indicates that they are undoubtedly members of the genus *Brucella*, thus rounding out the evidence pointing to a member of this group of bacteria as the incitant of the ulcerative valvular infection. The dense sclerotic process which also involved this aortic cusp, as well as the other cusps, which were not acutely inflamed, is believed to be the result of a much more remote infection, which was probably rheumatic.

Post-mortem culture of the heart's blood revealed *Br. melitensis*. Culture of the lesion on the aortic valve was contaminated by diphtheroids, *Br. coli*, *Br. fecalis*, and *Br. alcaligenes*. The only other findings of interest noted on microscopic examination were small areas of focal glomerulonephritis.

COMMENT

It is probable that the patient had been suffering from brucellosis for at least one year prior to his death. One can speculate that the prolonged insult to the aortic valve, already the site of rheumatic alterations, led to the eventual development of the endocarditis.

It is of interest to note that in this case, as in many of those reported by Call and associates,[3] the aortic valve was affected and an ulceration was present.

SUMMARY

A case of endocarditis, affecting a previously damaged aortic valve, occurring during a chronic infection due to *Br. abortus*, and associated with positive blood cultures for this organism, is reported.

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3. Call, J. D., Baggenstoss, A. H., and Merritt, W. A.: Endocarditis Due to Brucella: Report of Two Cases, Am. J. Clin. Path. **14:508**, 1944.
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Announcement

The American Heart Journal will be continued uninterruptedly as an independent monthly Journal under the editorial direction of leading cardiologists. It will not be the official organ of the American Heart Association after December, 1949.

The new Editor and Editorial Board will be announced in the December or the January issue.

Abstracts and Reviews

Selected Abstracts

Grossi, L., and Seitun, F.: Acquired Coaretation of the Aorta Near the Diaphragm. Cuore e circolaz. **32**:271 (Oct.), 1948.

The authors describe a case of acquired coarctation of the descending aorta in a patient affected by diffuse scleroderma. The coarctation was related to sclerodermic retraction of the diaphragm with diminution of the hiatus and constriction of both the aorta and the esophagus. Confirmation of the diagnosis was obtained by means of tomographic studies.

LUISADA.

Jones, S. H., Younghusband, O. Z., and Evans, J. A.: Human Parabiotic Pygopagus Twins With Hypertension: Report of a Case With Clinical, Psychologic, and Endocrinologic Observations. J. A. M. A. **138**:642 (Oct. 30), 1948.

This report relates the observations of the authors on a pygopagus, a set of twins conjoined at the buttocks. The fusion of the twins, Margaret and Mary, 34 years of age, resulted from fusion of anomalous sacral bones and of their perinea. A common anal orifice and rectum were present, with separate sigmoid colons. There were separate urethrae, vaginae and uteri, but the medial labiae were absent.

Margaret was thin and apprehensive, whereas Mary was stout and placid. Margaret had a Grade 2 hypertension, first discovered five months previously, and a systolic apical murmur was noted. She had also a leiomyoma of the uterus. She had had unilateral renal calculi at the age of 21 and had later been found to have a cystitis and urethral narrowing, for which dilatation had been performed. Mary had a mild labile hypertension which was normal at rest. Their mother had a marked hypertension.

The blood pressures of both twins showed generally parallel changes during their hospital course, Margaret's pressures being higher. The intravenous administration of tetraethylammonium chloride ("etamon chloride") to each of the sisters brought about a drop in the systolic and diastolic pressures of both, but the effect on Margaret's pressure was greater than that on Mary's even when the drug was administered only to Mary. This is indicative of increased vasomotor tone of the more hypertensive sister. The cold pressor test elicited rises in tension in each sister, but no crossed effect was noted; this is to be expected because vasomotor rather than chemical changes are involved in the cold pressor reaction. The sodium amytal and Mecholyl tests brought about significant pressure decreases in each sister individually; the lack of crossed effects with these procedures is apparently explained by the rapid removal of the drugs from the blood stream so that little or none reached the other sister. The urea clearance and phenolsulfonphthalein tests revealed evidences of renal damage in the more hypertensive twin; small amounts of phenolsulfonphthalein were found in the urine of the second sister even when the dye was administered to the other. After Iodopyracet injection was given intravenously to Margaret, her renal calices were not visualized by x-ray study and her bladder showed only poor concentration of the dye, whereas good visualization of Mary's urinary tract resulted; after administration of the dye to Mary, good visualization of Margaret's bladder was found.

The differences in the emotional make-up of the twins would indicate that emotional states are not mediated by way of the circulation. Although the parallelism of the blood pressure curves of the sisters suggests a humoral factor, this may have been due to similar responses to

environmental influences. Renal and tensional factors appeared to be of importance in the pathogenesis of Margaret's hypertension, while hereditary and humoral factors were apparently involved in the development of Mary's milder hypertension.

HANNO.

Blalock, A.: Surgical Procedures Employed and Anatomical Variations Encountered in the Treatment of Congenital Pulmonic Stenosis. Surg., Gynec. & Obst. **87**:385 (Oct.), 1948.

At the present time, there are only three general types of congenital cardiovascular defects which are amenable to surgical treatment: (1) patent ductus arterious, (2) coarctation of the aorta, and (3) an abnormality in which there is an inadequate pulmonary blood flow and in which mixed venous blood enters the arterial circulation.

The most frequently encountered condition of this third type is the tetralogy of Fallot. The severity of the cyanosis depends, in addition to other conditions, upon the degree of pulmonic stenosis and the degree of overriding of the aorta. The primary indication for the operation is an inadequate flow of blood to the lungs and an interventricular defect with an overriding aorta. The author performs the following anastomoses between the systemic and pulmonary arteries: (1) the proximal end of the right or left subclavian artery and the side of the right or left pulmonary artery, (2) the proximal end of the right or left subclavian artery and the distal end of the right or left pulmonary artery, (3) the proximal end of the carotid or innominate artery and the side or distal end of the right or left pulmonary artery, and (4) the side of the aorta and the side of one of the pulmonary arteries. The author prefers an anastomosis between the proximal end of the subclavian branch of the innominate artery and the side of one of the pulmonary arteries because the subclavian branch of the innominate artery when transposed makes a much more satisfactory angle with its parent vessel than is present when the subclavian branch of the aorta is used. The principle underlying all of the operative procedures is by-passing the point of stenosis in the pulmonary artery and allowing poorly oxygenated blood in the aorta to pass through the lungs. One should know preoperatively the position of the aorta, for this is of importance in determining the side on which the operation is performed. If the aorta descends on the right, and one wishes to use the subclavian branch of the innominate artery, the incision is made on the left. If the aorta descends on the right and one wishes to use the aorta, obviously the incision is made on the right.

The author presents several reasons why surgery should not be performed upon infants under the age of 2 years and he also gives an account of some of the anomalies of the blood vessels as observed in the course of operating. The mortality rate in patients 2 years of age and older with a typical tetralogy of Fallot is low. The danger is considerably greater when patients have associated complications such as rotation of the heart and cardiac arrhythmias. The majority of the patients who have survived the operative procedure are improved. The degree of improvement ranges from no limitations in activity to definite restrictions.

The author's series now totals 610 patients. There have been 108 deaths, an over-all mortality rate of 17.7 per cent. Twenty-seven of the deaths occurred during the operation, sixty-eight in the postoperative period and thirteen after discharge from the hospital.

BECK.

Smith, R. G., and Campbell, D. A.: Some Technical Considerations in the Arteriographic Examination of the Lower Extremity. Surgery, **24**:655 (Oct.), 1948.

The authors describe the technique they found most effective in the study of the state of the arterial tree in the lower extremity by means of arteriography. The patient is placed on a mattress on the floor in order to obtain exposures at six feet with the ordinary radiographic equipment. This is not possible if the subject lies on the table. Exposures of this distance are needed to visualize the entire arterial tree of the lower extremity with one injection. The site of injection over the femoral artery is anesthetized with 2 per cent procaine, and 30 c.c. of 35 per cent Diodrast are injected into the artery through a long 18-gauge, short-beveled needle. Previously the proximal portion of the artery is compressed against the pubic ramus. When 25 c.c. have been injected,

the first exposure is made. Digital pressure on the artery is then released for four seconds, the remaining 5.0 c.c. of solution are injected, and the second exposure is made.

ABRAMSON.

Morrison, M., Richter, I. H., and Loewe, L.: Increased Platelet Clumping in Thromboembolic Disease. Am. J. Clin. Path. **18**:879 (Nov.), 1948.

The authors studied routine differential blood films made on glass slides. The presence of blood platelet clumps and the number of platelets per clump were noted. Fewer than ten platelets per clump was considered normal; more than ten, abnormal.

In 100 control subjects, clumping was normal in 92 per cent and increased or abnormal in 8 per cent. Of 100 patients with various types of thromboembolic disease, clumping was normal in 19 per cent and increased in 81 per cent.

A correlation was attempted between increased platelet clumping and (1) thrombocytosis and megakaryocytosis, (2) increased erythrocyte sedimentation rate, (3) leucocytosis, and (4) fever. The authors felt that while thrombocytosis is usually associated with an increased tendency to clumping of platelets, such a tendency is not necessarily associated with, or caused by, thrombocytosis. A study of sternal bone marrow in fifty-one consecutive unselected patients was interpreted to indicate that megakaryocytosis parallels thrombocytosis in its relationship to clumping tendency. It was further found that while clumping is frequently associated with leucocytosis and/or increased sedimentation rate and sometimes with fever, this correlation is not consistent.

Because of the large number of patients in the thromboembolic group with increased clumping in contrast to the small number found in the control group, the authors conclude that this simple method of grading the tendency of blood platelets to clump may be of value in indicating a tendency of certain persons to develop thrombosis and may make it possible for these persons to be protected by the use of anticoagulants.

BEIZER.

Evans, L. R., and White, P. D.: Massive Hypertrophy of the Heart With Special Reference to Bernheim's Syndrome. Am. J. M. Sc. **216**:485 (Nov.), 1948.

The study of thirty-three hearts weighing more than 750 grams showed that hypertensive heart disease was the etiological agent in sixteen, while rheumatic heart disease with mitral stenosis alone, or with aortic valve involvement, was responsible for eight and for the largest of the hearts examined. In the remainder the causes of enlargement were: calcareous aortic stenosis in three, and, in one each, hypertension and rheumatic heart disease, coronary arteriosclerosis, arteriosclerosis of the aorta with aneurysm, syphilitic aortitis with aortic regurgitation, Ayerza's disease, and chronic myocarditis.

In the hearts of the group with left ventricular hypertrophy (twenty-two patients), no instance could be found of isolated early signs or symptoms of right-sided failure. The authors have concluded from this analysis and from prior experience that they have yet to encounter any unquestionable case of so-called Bernheim's syndrome. It would appear sensible to drop this designation unless proof can be adduced to support it.

DURANT.

Burchell, H. B.: An Evaluation of Esophageal Electrocardiograms in the Diagnosis of Healed Posterior Myocardial Infarction. Am. J. M. Sc. **216**:492 (Nov.), 1948.

Experience with esophageal electrocardiography in attempting to elucidate the significance of a Q wave in Lead III has been scattered over the past ten years. The use of small but heavy electrodes with thin, flexible lead wires has made the problem easier for the patient, who may either swallow the electrode like a capsule or allow it to pass down the throat when it is introduced through the nose. For comparison of esophageal electrocardiograms made at different levels it has been helpful to use multiple electrodes at fixed distances along the small-caliber flexible plastic tube which carries the insulated lead wires. A group of fifty cases in which esophageal electrocardiograms were made has been chosen for the purpose of determining the probability of obtaining diagnostic tracings in cases in which the history and electrocardiograms at the time of an acute episode indicated previous acute myocardial infarction and in cases in which only angina pectoris or a deep Q_3 was present.

As a result of these studies it has been concluded that electrocardiograms made with the electrode in the lower part of the esophagus and stomach are sometimes of great value in confirming a diagnosis of healed posterior myocardial infarction, but sometimes they are normal or are not definitely diagnostic even when the heart is known to contain a scar in the posterior myocardial wall. Esophageal electrocardiograms which might be regarded as diagnostic of old posterior myocardial infarction, particularly those with QS deflections followed by a deeply inverted T wave, have usually been associated with a suggestive or diagnostic Q_2Q_3 pattern in the standard leads in this study. While the transitional zone through which the types of ventricular complex characteristic of atrial levels and of ventricular levels are obtained is usually narrow, in some instances the former type of complex may tend to persist when the atrial complex contains no intrinsic type of deflection.

When the esophageal leads are used to elucidate the clinical significance of a deep Q_3 in cases in which this is the only finding leading to the suspicion of previous myocardial infarction, the findings are frequently of equivocal nature. DURANT.

Courter, S. R., Felson, B., and McGuire, J.: Familial Interauricular Septal Defect With Mitral Stenosis (Lutembacher's Syndrome). Am. J. M. Sc. **216**:501 (Nov.), 1948.

Familial congenital interauricular septal defect complicated by mitral stenosis is described apparently for the first time by the authors. This disorder was found in two sisters, 21 and 26 years of age, respectively. In a review of the literature the authors were unable to find any mention of familial Lutembacher's syndrome, and also no report of a familial occurrence of uncomplicated interauricular defects. DURANT.

Porter, W. B.: The Probably Grave Significance of Premature Beats Occurring in Angina Pectoris Induced by Effort. Am. J. M. Sc. **216**:509 (Nov.), 1948.

From an extensive experience with the electrocardiogram associated with exercise in cases of angina of effort, an experience which has extended over more than eight years, the author states that the most significant change during induced attacks has been the occurrence of premature ventricular beats in four patients in whom normal rhythm was present before and after the induced episode. Three of these patients had few signs of cardiovascular disease and resting electrocardiograms were equivocal in all four. The premature beats occurred during the period of acceleration of heart rate and at the peak of chest pain, disappearing with rest and cardiac slowing. This is in contrast to the general rule that extrasystoles are increased during the post-acceleration or slowing period following induced tachycardia. It is suggested by the author that the occurrence of premature beats, especially pulsus bigeminus, under these circumstances may have grave prognostic significance. He feels, however, that a larger series of cases must be studied before final conclusions can be drawn. A conservative dose of quinidine sulfate, consisting of 0.2 to 0.4 Gm., given three times daily and equally spaced during the period of physical activity, may be used profitably in these patients since in two of those reported, the exercise tolerance was greatly increased thereby. DURANT.

D'Alton, C. J., Darling, R. C., and Shea, E.: The Insensible Loss of Water in Congestive Heart Failure. Am. J. M. Sc. **216**:516 (Nov.), 1948.

Congestive heart failure is characterized by a marked disturbance in fluid balance. While the failure of the kidneys to excrete water and salt in this condition has been extensively studied, water loss by other routes has been less thoroughly investigated. For this purpose fourteen determinations of the insensible weight loss, partitioned into its several parts, were accomplished. Eight of these were carried out on patients with heart disease, including three comparisons of the same patient before and after recovery from severe decompensation. From these measurements the quantity of insensible perspiration was found not to change significantly when the circulatory status of an individual was altered by cardiac decompensation, although the amount lost by way of the lungs followed the pulmonary ventilation. The absolute quantity of insensible perspiration (skin) in these patients and a few others with various diseases correlated only very roughly with body size, and seemed to be characteristic of the individual. The range of individual measurements was large but well within the reported range in all instances. The palmar sweat secretion and,

by inference, the solar, together contributed little to the total insensible water loss under the conditions of the study, being less than 5 per cent of the total. DURANT.

Schlichter, J. G., Wilburne, M., and Grossman, M.: The Use of Acetylcholine in the Objective Determination of Circulation Time in Man. Am. J. M. Sc. **216**:523 (Nov.), 1948.

In the course of a study of the effects of acetylcholine, it was noted that an accurate objective determination of the circulation time in unanesthetized normal dogs and anesthetized open-chested animals may be obtained by the use of this substance. The circulation time obtained with this substance is shorter, shows fewer variations, and appears superior to most methods applicable to animals. One distinct advantage is that an unequivocal end point can be determined electrocardiographically.

The results indicated that acetylcholine also offers a clear end point for the objective determination of circulation time in man. The doses used caused varying degrees of sinus slowing or asystole. The minimal dose evoking such response varied in the different patients, but the average was 40 milligrams. Inasmuch as doses of more than 60 mg. were not administered, failure to obtain a circulation time measurement in some patients may have been due to inadequate doses. The action of the drug on the heart, on the basis of animal experiments, appears to be a direct one whereby the acetylcholine passes via the coronary vessels to the sinus node and the A-V junction. A correlation of the circulation time with other clinical and laboratory findings has shown that the normal circulation time varies between 1.2 and 6 seconds. A circulation time over 7 seconds was found to be definitely abnormal. Compared with other methods, acetylcholine yields a distinctly shorter circulation time. The small volume and the short duration of the injection reduces the range of variation seen with the sodium cyanide, thiamine, and Diodrast methods.

The only serious objection to the use of this test for the determination of the circulation time in man is the induction of multiple premature systoles and auricular fibrillation. The latter was observed in two cases. Both of these patients had hypertension and coronary sclerosis and one was also markedly anemic. The margin of safety may be very small. In one case, 20 mg. had no effect whereas 25 mg. produced asytole followed by auricular fibrillation. In both cases in which auricular fibrillation occurred the mechanism was broken and sinus rhythm re-established by the administration of oral quinidine. Atropine injections and oxygen inhalation did not abolish the arrhythmia. It is concluded that while acetylcholine may be used for simple, accurate, and objective measurements of circulation time in man, it cannot be regarded as an innocuous procedure for the patient. DURANT.

Bine, R., Jr., and Friedman, M.: Observations Concerning the Effects of Blood Upon the Action of a Digitalis Glycoside. Am. J. M. Sc. **216**:534 (Nov.), 1948.

In a previous study, it was found possible, by means of the embryonic duck heart preparation, to detect as little as 0.05 microgram of a digitalis glycoside per cubic centimeter of Tyrode's solution. The extreme sensitivity of this preparation to glycoside in Tyrode's solution suggested the possibility that perhaps minute amounts might be detected in blood also. In order to standardize this type of detection, however, it was thought necessary to determine separately the effects of blood cells and serum of whole blood.

It was found that rat and human blood sera inhibited markedly the effect of the glycoside. This retardation of action, however, was not marked at moderate concentration of the glycoside (1.0 microgram per cubic centimeter), but only at low concentrations (below 1.0 microgram per cubic centimeter). It is suggested that the retardation in serum is not due primarily to the action of the serum on the drug, but rather to the inability of the embryonic heart to respond quickly to a medium low in ionized calcium (about 5.0 mg. per 100 c.c.). It was of particular interest, however, that as little as 0.1 microgram of glycoside in 1.0 c.c. of human serum could be detected by means of the preparation. Perhaps even more important was the finding that the time of occurrence of the "digitalis effect" depended upon the concentration of the glycoside in the serum. This last finding allows the possibility of making quantitative assays of the content in any given serum sample suspected of containing it. DURANT.

Bennett, I. L., Jr., and Hyeman, A.: Paroxysmal Hypertension Associated With Tabes Dorsalis. Report of Three Cases. Am. J. Med. **5**:729 (Nov.), 1948.

The purpose of this article is to report three additional cases of paroxysmal hypertension associated with tabes dorsalis. In one of the cases presented, the unfamiliarity with this association led to a needless surgical exploration for a pheochromocytoma. The authors point out that gastric crises are not always associated with the bouts of hypertension. Gastric crises were present in only one of their patients and in this instance the attack consisted only of nausea and vomiting unaccompanied by pain. The hypertension was entirely asymptomatic in the second patient and in the third patient the paroxysms of hypertension were not accompanied by symptoms except for occasional associated lightning pains. Penicillin therapy appeared to have a beneficial effect on the hypertensive crises in only one of the patients. They were unable to find any certain means of precipitating hypertension in their patients. The histamine test for pheochromocytoma was uniformly negative. The authors believe that paroxysmal hypertension is simply one of the disturbances of the autonomic nervous system that may occur in tabes dorsalis.

KLINE.

Massey, F. C., and Drake, W. L., Jr.: Spontaneous Rupture of the Heart Due to Myocardial Infarction. Am. J. Med. **5**:775 (Nov.), 1948.

The authors report the case of a 42-year-old white man who was hospitalized because of a myocardial infarction. Serial electrocardiograms localized the infarction to the anterior surface of the left ventricle. Twelve days after admission the patient was being examined routinely. Suddenly and without warning the patient tensed all his muscles, straightened out rigidly, the neck dropped backward in opisthotonic fashion, and tonic and clonic convulsions shook him for a few seconds. During this time one of the authors was auscultating the heart. No friction rub was heard before this spectacular episode, but immediately after its inception an intense, grating pericardial rub was audible from the third left intercostal space down to the apex. Just prior to the appearance of the pericardial rub auscultation of the heart was interrupted in order that a question might be answered so that if rupture of the ventricle occurred at this instant it was not actually heard. Within three minutes after the onset of the episode the patient was dead. Post-mortem examination of the heart revealed a jagged, vertical tear on the anterior surface of the apex parallel to, and immediately to the left of, the interventricular septum. The defect was 2.5 cm. in length.

KLINE.

House, R. K.: Diffuse Interstitial Myocarditis in Children. Am. J. Path. **24**:1235 (Nov.), 1948.

The author reviews four cases of diffuse interstitial myocarditis in infants ranging in age from 3 weeks to 13 months. The clinical course was short and was featured by fever, cyanosis, dyspnea, and anorexia. Cardiac enlargement and tachycardia, "low T waves in all leads," pulmonary congestion, and enlargement of the liver suggested some form of myocarditis. These children were well nourished and showed no evidence of congenital defect, nor anything to account for the cardiac hypertrophy found in all cases.

Microscopically there was a diffuse interstitial cellular infiltration, primarily lymphocytic, accompanied by widespread interstitial edema, but little damage to individual myocardial fibers. In two cases there was an additional endocardial fibrosis, but in only one was there any evidence of patchy fibrosis in the myocardium. The lungs in all cases showed a bronchopneumonia which was interpreted as being secondary and terminal.

A review of the history showed that upper respiratory infection had developed in at least three of the four cases. Sulfonamide therapy employed in one case appeared to be a factor too remote for consideration.

All the recorded causes, proved or suspected, in "diffuse interstitial myocarditis" were reviewed and none appeared applicable to these cases. The report is of interest in revealing in infants a type of myocardial disease generally expected in adults. On the other hand, the causative factors remain equally obscure.

GOULEY.

Nahum, L. H., and Hoff, H. E.: Nature of the Precordial Electrocardiogram. Am. J. Physiol. **155**:215 (Nov.), 1948.

Right and left apical precordial leads were recorded in fifteen dogs at rest, and following warming, cooling, and the application of potassium chloride to various cardiac regions. The authors assume that the precordial electrocardiogram represents a record composed by interference of opposing electrical forces either proximal or distal with respect to the exploring electrode. Their interpretation applies to the QRS deflection as well as to the T wave. The proximal zone represents the area in the immediate vicinity of the precordial electrode (epicardial or endocardial). The distant region usually includes the base of the heart. An intermediate zone is described, which when cooled, warmed, or treated with potassium chloride, influences the precordial electrocardiogram but little. As the electrodes were placed at the apical area, precordial electrocardiograms of the kind obtained are interpreted as base-apex interference records.

HECHT.

Parson, Wm., Mayerson, H. S., Lyons, C., Porter, B., and Trautman, W. V., Jr.: Effect of the Administration of Adrenalin on the Circulating Red Cell Volume. Am. J. Physiol. **155**:239 (Nov.), 1948.

Simultaneous plasma and red cell volume determinations, using T-1824 and radiolabelled red cells, were performed on five subjects following the subcutaneous injection of 1.0 mg. of adrenalin. A good clinical epinephrine response was noted in all, but no changes in plasma volume, red cell volume, total blood volume, hematocrit readings, hemoglobin, and plasma protein concentration could be demonstrated. It is assumed that in man no appreciable blood cell reserves are available for emergency mobilization.

HECHT.

Mayerson, H. S., Lyons, C., Parson, Wm., Nieset, R. T., and Trautman, W. V., Jr.: Comparison of Results of Measurements of Red Blood Cell Volume by Direct and Indirect Technics. Am. J. Physiol. **155**:252 (Nov.), 1948.

Determining the volume of packed red cells, the use of radioactive red cell measurements with P_{32} and the determination of plasma volume with T-1824 yielded concomitant measurements of red cell mass, plasma volume, and total blood volume in ten normal subjects and in thirty-five patients suffering from a variety of diseases not directly related to the cardiovascular system. If the hematocrit values were corrected for plasma trapped between the cells by a factor 0.915, good agreement was obtained between the "true" blood volume obtained from determinations by red cell-P_{32} and dye-plasma methods and blood volumes obtained from corrected hematocrit readings and either red cell or plasma volume determination. It is assumed that the amount of blood present in the small vessels (with generally lower hematocrit values) is not large enough to affect greatly the estimation of blood volume calculated from the dye and the corrected hemotocrit reading under relatively normal conditions.

HECHT.

Berenson, G.: Value of Routine Fluorograms as a Measure for Detecting Cardiac Abnormalities. Am. J. Pub. Health **38**:1564 (Nov.), 1948.

This is the report of 14,235 miniature films (35 mm.) taken as routine fluorograms of marine and naval personnel at a military camp in North Carolina in 1947. Although the ages varied from 17 to 60 years, the majority were young marines just entering military life. In thirty-one subjects cardiovascular abnormalities were noted. In eighteen of these, including three civilians, cardiac enlargement on a hypertensive basis was present. Three instances of dextrocardia without situs inversus were noted. Two patients had a funnel chest causing enlargement. Dextroposition of the aorta and coarctation were present in one patient each. Various aortic and mitral configurations were seen. Twenty-two patients had noncardiovascular diseases of the chest, including pulmonary tuberculosis in ten patients.

The author concludes that it is possible to detect cardiac abnormalities on routine fluorograms, accurate diagnosis requiring confirmation by further clinical investigation. It is suggested by this series that the number of patients with demonstrable cardiac abnormalities in routine fluorograms is greater than the number of persons with tuberculosis in a given population. The author, therefore, emphasizes the importances of discovery of heart disease by mass fluorography.

WAIFE.

Moyer, J. H., and Ackerman, A. J.: Hereditary Hemorrhagic Telangiectases Associated With Pulmonary Arteriovenous Fistula in Two Members of a Family. Ann. Int. Med. **29**:775 (Nov.), 1948.

The authors describe the physical, radiologic, and laboratory findings in two brothers 29 and 26 years of age, respectively, in whom a clinical diagnosis of pulmonary arteriovenous fistula complicating hereditary hemorrhagic telangiectases was made. In each instance, the diagnosis of the pulmonary lesion was confirmed by angiographic studies. In the older of the two brothers, cyanosis, clubbing of the fingers, hyposaturation of the blood with oxygen, compensatory polycythemia, increased blood volume, and extracardiac murmurs were lacking. By contrast, in the younger brother, all these findings were present. This difference was attributed to the larger communications which were demonstrable between the pulmonary arteries and veins in the latter instance, which resulted in an increased amount of unaerated blood being shunted back to the left heart. In the cyanotic patient, all the primary and secondary manifestations of the venous-arterial shunt were completely eliminated following a successful unilateral pneumonectomy.

The authors emphasize the association of these pulmonary vascular lesions with hereditary hemorrhagic telangiectases of the skin and relate them both to a common congenital fault which results in the formation of new vascular buds with consequent direct communications between arterioles and veins which circumvent the normal capillary bed. WENDKOS.

Levine, H. D.: Abnormal Rapid Rhythms Associated With Digitoxin Therapy. Ann. Int. Med. **29**:822 (Nov.), 1948.

By means of serial electrocardiographic records in seven patients who had received varying amounts of digitoxin for the treatment of heart failure, it was possible to demonstrate that serious rhythms, such as ventricular tachycardia and A-V dissociation, can result from the toxic action of this drug. In most instances, excessive amounts of the drug could be held responsible, but in a few of the cases, the patients were receiving doses which are ordinarily considered to be therapeutic. As with crude digitalis preparations, the toxic rhythms produced by digitoxin developed at times without any of the usual premonitory gastrointestinal or visual disturbances indicative of digitalis intoxication. Their occurrence should, therefore, be suspected when, in the presence of auricular fibrillation, a previously irregular ventricular rhythm suddenly becomes regular or when, in the presence of normal sinus rhythm, the rate should suddenly accelerate.

WENDKOS.

Massie, E., Huguley, C. H., and Stillerman, H. S.: The Heart in the Terminal State: Effect of Intracardiac Epinephrine. Ann. Int. Med. **29**:838 (Nov.), 1948.

Electrocardiograms were taken on thirty-four patients before, at the time of, and after clinical death. Slowing of the cardiac rate was almost a constant finding with subsequent sino-auricular node depression and resultant auriculoventricular nodal rhythm appearing in over one-third of the cases. Auriculoventricular and intraventricular block in various degrees was extremely common. Evidences of ventricular irritability were manifested by the frequent occurrences of ventricular fibrillation, tachycardia, and flutter along with ventricular extrasystoles from single and multiple foci. Auricular fibrillation did not appear terminally except in those instances where it had been present previously. The terminal complex in the electrocardiogram represented ventricular activity in twenty-seven patients and auricular activity in seven. The terminal ventricular complexes often assumed bizarre shapes with marked variation in form, amplitude, and duration.

Attempts at cardiac resuscitation with intracardiac epinephrine following cessation of heart activity were made in eighteen patients, including eleven attempts in which the drug was injected into the cardiac chambers and nine in which it was infiltrated into the ventricular myocardium. The latter method was more successful, producing an effect in five patients (56 per cent), whereas the former accounted for only two responses (18 per cent). In only two patients was there restoration of regular ventricular beats; in one of these the cardiac activity continued for thirty-six minutes after respiration had ceased. The authors suggest that if intracardiac epinephrine is to be life-saving, it should be given, if possible, before complete cardiac cessation occurs and before the heart muscle and vital cerebral centers have been deprived of oxygen for too long a period.

WENDKOS.

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NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES TO BE HELD IN WASHINGTON IN JANUARY

A National Conference on Cardiovascular Diseases will take place in Washington, D. C., January 18-20, 1950, under the joint sponsorship of the American Heart Association and the National Heart Institute. Dr. H. M. Marvin, President of the Association, and Dr. C. J. Van Slyke, Director of the National Heart Institute, will be the Co-Chairmen.

The purpose of the Conference is "to investigate, define and develop immediate and long-range programs designed to meet the problems of research, education, and community service posed by diseases of the heart and circulation, and to coordinate the efforts of all groups concerned with these problems, with a view to gaining the most effective use of their resources for all the members of the community."

Dr. Paul D. White, Executive Director of the National Heart Institute, was elected Chairman of a steering committee to plan the Conference. Dr. White is a former President of the American Heart Association.

The Conference is to be comprised of members representing the various medical disciplines and the ancillary professional fields concerned with a cardiovascular program. It will have three main sections: Technical Knowledge and Research, Community Service, and Education. Described as a "working," not a "talking" Conference, the three-day meeting is expected to develop a concrete program of action to correlate an all-out national attack on the heart disease problem embracing the resources of all voluntary and official agencies in the field.

EXECUTIVE COMMITTEE MEETING

A new set of recommended standards and minimum requirements for cardiovascular clinics has been prepared by the Cardiovascular Clinic Committee and will be presented to the Board for approval at its December meeting.

Dr. Paul D. White was appointed the Association's official delegate, and Dr. H. M. Marvin, deputy, to the First International Congress on Cardiology to be held in Paris in September, 1950.

Dr. Frederick Lewy has been employed to carry out a two-year study of community rheumatic fever programs for the American Council on Rheumatic Fever.

New affiliated heart associations approved, in addition to those listed in the October issue, include the Massachusetts Heart Association and the Middle Tennessee Heart Association.

A. W. ROBERTSON CHAIRMAN OF 1950 HEART CAMPAIGN

Mr. A. W. Robertson, of Pittsburgh, serving his second term as Chairman of the Board of the Association, has consented to be General Campaign Chairman of the 1950 Heart Campaign. Mr. Robertson is Chairman of the Board of Westinghouse Electric Corporation and has long been active in civic and welfare activities.

Mr. Winthrop W. Aldrich will again serve as Campaign Treasurer, and Secretary of Labor Maurice Tobin, as Chairman of the Labor Committee.

GRANTS-IN-AID FOR RESEARCH

Applications for grants-in-aid for cardiovascular research in 1950-1951 must be filed by December 15, 1949. A total of forty-nine applications for Research Fellowships and Established Investigators had been received by the September 15 deadline.